THE PATHOGENESIS OF OSTEOPOROSIS *

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OSTEOPOROSIS may be defined as a reduction in the amount of bone without any change in its chemical composition. Considering bone as a tissue rather than as an organ, osteoporosis is a disease of bone quantity rather than bone quality. In this respect it differs from osteomalacia, the essential feature of which is a change in bone quality due to a reduction in the ratio of mineral to organic material. Osteoporosis and osteomalacia have, however, a similar effect upon the mechanical function of bone because they both weaken the skeletal parts affected. The two conditions often coexist, particularly in steatorrhæa (Atkinson et al. 1956, Lichtwitz et al. 1959). Fig. 1 illustrates this general concept.

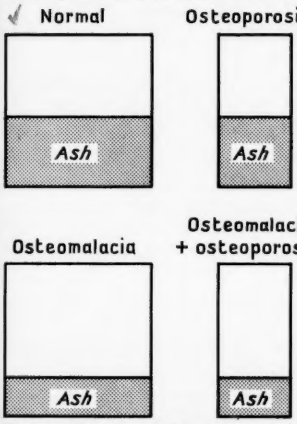

Fig. 1—Diagrammatic representation of principal metabolic abnormalities of skeleton.

Classification

Osteoporosis may be generalised or localised. It may be associated with some well-recognised metabolic abnormality or it may appear as a disease in its own right. The following ætiological classification is therefore appropriate.

Generalised Osteoporosis

1. Primary
2. Secondary to:
   - Hyperthyroidism
   - Hyperparathyroidism
   - Cushing's syndrome
   - Diabetes mellitus
   - Acromegaly
   - ? Others

Localised Osteoporosis

- Immobilisation
- Sudeck atrophy
- Rheumatoid arthritis

The observations which follow deal mainly with primary osteoporosis, but may also be applicable to some of the secondary forms. Except where specifically indicated no attempt will be made to distinguish between spinal (trabecular) and peripheral (cortical) osteoporosis (Barnett and Nordin 1960). Most of the cases reported here are of the spinal type.

The pathogenesis of osteoporosis is unknown, but several hypotheses have been advanced. Because the essential feature is a reduction in bone mass, osteoporosis could be due to a diminished rate of new-bone formation, an increased rate of resorption, or a combination of the two.

* Based on a lecture given at the Postgraduate Medical School of London on Nov. 4, 1960.

Reduced Bone Formation

The current view that osteoporosis is due to diminished formation of bone matrix dates from a paper by Albright et al. (1941b), though it had previously been suggested by Pommer in 1885. Albright and his colleagues drew attention to the large number of postmenopausal women (in many of whom the menopause had been artificially induced) in their osteoporosis series, and suggested that gonadal deficiency might be the caues of the disease. Later in the same year Albright et al. (1941a) postulated that the osteoporosis of Cushing's syndrome was due to inhibition of bone-protein synthesis by excess " S " hormone.

Subsequently, Albright and Reifenstein (1948) assembled the evidence for the hypothesis that virtually all forms of osteoporosis are due to impaired new-bone formation arising from a defect in either the osteoblasts or in the processes of protein synthesis. They emphasised the association of the condition with negative nitrogen balance, as in hyperthyroidism, and with gonadal insufficiency—e.g., ovarian agenesis—and they published calcium balances which demonstrated an improved balance after the administration of œstrogens and androgens. They also described and classified the causes of osteomalacia, implying that this disease was due ultimately to negative calcium balance attributable to malabsorption in vitamin-D deficiency and to hypercalciuria in renal tubular acidosis.

In the twelve years since the publication of this classical monograph, much work has been done which must modify the basic assumptions underlying Albright's view. In particular, the demonstration by Carlsson and Lindquist (1955) of a direct calcæmic action of vitamin D on bone has shown that vitamin-D deficiency and calcium deficiency do not necessarily produce the same end-result. We are beginning to appreciate the vital role of the skeletal mineral in sustaining the concentration of calcium in plasma even in the face of negative calcium balance (Nordin 1960a). Moreover, the direct measurement of bone " accretion-rate " with tracers has usually failed to show any reduction in osteoporosis (Heaney and Whedon 1958, Nordin 1959a, Fraser et al. 1960), though Eisenberg and Gordan (personal communication), using stable strontium, report that the mean " accretion-rate " in a group of osteoporotics is significantly less than normal. The time is therefore ripe to question Albright's hypothesis and to consider whether osteoporosis could be due to an increase in the rate of bone removal.

Increased Bone Resorption

A possible cause of increased bone resorption is long-continued negative calcium balance. The question therefore arises whether the histological picture of osteoporosis can be produced by negative calcium balance in animals.

EXPERIMENTAL CALCIUM DEFICIENCY

Most writers have assumed with Albright that vitamin-D deficiency produces rickets by interfering with calcium absorption and that calcium deficiency must therefore have the same effect. This is probably incorrect. Rickets is most easily produced in rats with a vitamin D-deficient, high-calcium low-phosphorous diet which reduces the Ca × P product in plasma. Calcium deprivation without

deficiency of vitamin D, on the other hand, has been shown to produce osteoporosis in a variety of laboratory animals. For example, Light and Frey (1941) reported the results of their experiments as follows:

"A diet adequate with respect to vitamin D and phosphorus but deficient in calcium will produce a skeletal structure which is hard, but light and fragile, in young growing animals. The thin-walled bones, showing no evidence of rickets, do not bend easily, have a nearly normal bone ash and are not enlarged at the ends . . . In rabbits we find that vertebræ are the common site of fractures."

Many other workers have reached similar conclusions and their work has been reviewed elsewhere (Nordin 1960a). The most recent confirmatory work is that of Greaves and Scott (1959) and Harrison and Fraser (1960).

CALCIUM INTAKE AND CALCIUM REQUIREMENT

Since calcium deficiency produces osteoporosis in animals, it is natural to suggest that the same might be true in man. It is commonly assumed, however, that the calcium intake of the great majority of inhabitants of the western world is ample for their requirements, simply because the mean intake is higher than the mean requirement.

The mean calcium intake of the adult population of the United Kingdom was stated in the National Food Survey for 1953 to be about 1200 mg. per head per day. Our 92 control subjects had the same mean intake (Nordin 1960b). This figure is higher than those recommended by the National Research Council of the U.S.A. and the British Medical Association Committee on Nutrition in 1950 (800 mg.). This appears on the face of it to be quite adequate. The coefficient of variation, however, is 27%. Assuming a normal distribution, this signifies that about 5% of the population is eating less than 500 mg. of calcium per day. If we assume the mean body-weight of the adults to be 65 kg. (which was also the mean weight of our control subjects) then the mean intake is 18·5 mg. per kg. per day. The 95% limits extend from 8·5 to 28·5 mg. per kg. per day and the 99% limits from 3·5 to 33·5 mg. per kg. per day.

The calcium requirement of adults can be defined as the amount of calcium required to preserve calcium balance. This means, with present techniques, the amount of dietary calcium which offsets the loss into the fæces and urine. It is probably an underestimate because it takes no account of calcium loss through the skin, which may be of the order of 100 mg. per day, or even more during heavy sweating (Malm 1959). The mean intake at which calcium balance is achieved in normal subjects has been found by many workers to be about 10 mg. per kg. per day (Sherman 1952, Mitchell and Curzon 1939). The variation around this mean figure, however, has never been satisfactorily established.

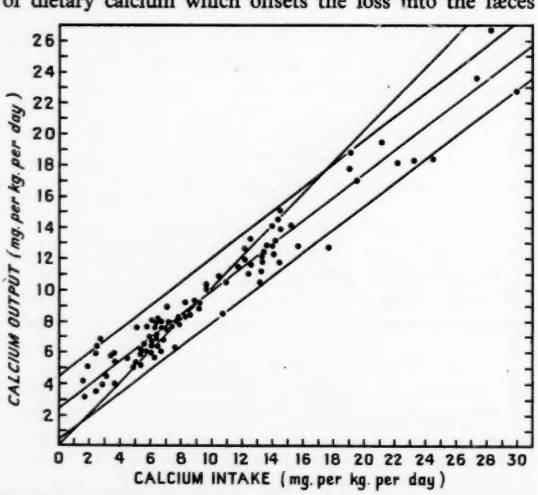

Fig. 2—Regression of calcium output on calcium intake in 92 calcium balances on normal subjects showing the mean and 95% confidence limits.

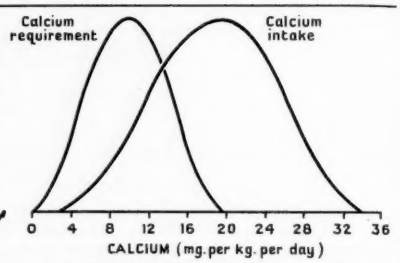

Fig. 3—Distribution of calcium requirement (calculated from data of fig. 2) and calcium intake (calculated from National Food Survey for 1953).

Fig. 2 shows the regression of calcium output on calcium intake in 92 balance studies on normal subjects collected from the recent literature (Nordin 1960b, c). The regression of Y on X and the 95% limits can be expressed by the formula: $Y = 0{\cdot}74\,X + 2{\cdot}41 \pm 2{\cdot}12$.

The mean value at which output and intake are equal—i.e., the mean calcium requirement of this group of normal subjects—is 9·3 mg. per kg. per day. Fig. 2 shows that this is the value at which the 45° line intercepts the mean regression line. The 95% limits are rather wide, however, and calculation shows that 95% of this population require between 1·0 and 17·6 mg. per kg. per day. 2·5% require more than 17·6 mg. per kg. per day, and 1% require more than 19·0 mg. per kg. to remain in calcium balance.

Clearly there is a considerable overlap between calculated calcium intake and calculated calcium requirement, and an attempt has been made in Fig. 3 to represent the distribution of these two variables. Calculation shows that if they vary independently, then about 8% of the population are taking insufficient calcium, even when no allowance is made for calcium losses through the skin.

These theoretical considerations do not, of course, take into account "adaptation" to low calcium intakes. It is certainly true that most normal people can adapt themselves to low calcium intakes by means of a reduction in urinary excretion, or by an increase in intestinal absorption, or by a combination of the two (Walker et al. 1948, Jackson and Dancaster 1959). That many subjects can adapt, at least partially, to low calcium intakes does not signify that everyone can do so. Malm (1958) has shown conclusively that some subjects on low intakes cannot adapt, and hence remain in negative calcium balance for years on end. One must therefore consider the possibility that in people who are unable to adapt their calcium requirement to their calcium intake osteoporosis finally develops.

NEGATIVE CALCIUM BALANCE IN CLINICAL OSTEOPOROSIS

If osteoporosis were due to negative calcium balance over a long period one would expect to find in osteoporotic patients evidence of inadequate calcium intake, malabsorption of calcium, or hypercalciuria. There is now some evidence that these factors are present.

Calcium intake.—Dietary intake is always difficult to assess, but the calculation of calcium intake is perhaps subject to less error than that of some other nutrients, since the only foods which really need to be considered are

TABLE I—DIETARY INTAKE OF CALCIUM AND PROTEIN (±2 S.E.) IN 71 OSTEOPOROTIC AND 96 NORMAL SUBJECTS IN THE U.K. AND 71 OSTEOPOROTIC AND 47 NORMAL SUBJECTS IN THE U.S.A. (Unpublished American data kindly supplied by Dr. Richmond Smith.) (Differences between osteoporotics and controls all significant; $P < 0.01$)

Observer	Calcium intake (mg. per kg. per day)		Protein intake (mg. per kg. per day)	
	Osteoporosis	Control	Osteoporosis	Control
Nordin (1960b)	13·4±1·5	17·9±1·3	1·02±0·08	1·28±0·09
Smith (U.S.A.)	9·9±1·1	12·8±1·8	1·02±0·06	1·16±0·09

milk, bread, and cheese. Nonetheless, the error must be considerable in any given subject, and it is desirable to study relatively large groups.

Table I shows the dietary intake calculated from diet histories obtained by professional dietitians in the Western Infirmary from 71 patients with primary osteoporosis without steatorrhœa and from 92 control subjects. The two groups are of similar age and sex (Nordin 1960c). The mean calcium intake of the patients is significantly lower than that of the controls, whose intake is very close to the national average (National Food Survey for 1953). Similar observations from Smith in the U.S.A. are shown in the same table. The American calcium-intake figures are lower than ours, probably because their bread is not "fortified" with calcium carbonate. The difference in

TABLE II—ANALYSIS OF 231 CONSECUTIVE DIET HISTORIES

X-ray score*	Calcium intake	
	<1 g.	>1 g.
<169 (osteoporosis) ..	61	6
>168 (no osteoporosis) ..	162	52

*See Barnett and Nordin (1960).

protein intake between the two groups in each series could be due to differences in milk consumption.

In table II, the X-ray findings are compared with the diet histories in 231 consecutive subjects without steatorrhœa. It will be seen that calcium intakes over 1 g. daily are very rarely associated with osteoporosis, but that lower intakes may or may not be associated with it. This would be expected if osteoporosis were due to negative calcium balance occurring in individuals unable to adapt to a low calcium intake ($\chi^2 = 13$: $P < 0.001$).

Urine Calcium

The difference in calcium intake between osteoporotic patients and controls would be of doubtful significance if it were associated with a corresponding difference in urinary calcium excretion. This, however, is not the case. On the contrary, calcium excretion in our patients with osteoporosis tends to be higher than in the controls (Nordin 1960b, c). Fig. 4 shows the ratio of calcium to creatinine (Ca/Cr) (Nordin 1959b) in random samples

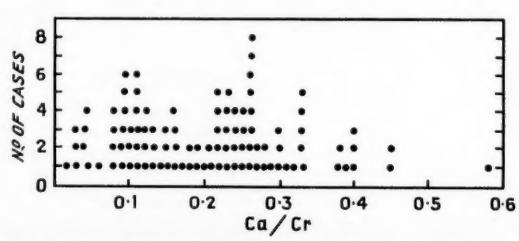

Fig. 4—Urinary calcium/creatinine ratio in 102 cases of osteoporosis. (Normal range: 0·03–0·28.)

from 102 cases of osteoporosis. A ratio over 0·30, indicating a high urine calcium, was observed in 21 of these patients. There is just a suggestion in fig. 4 that the distribution of Ca/Cr values is bimodal. Conceivably, there are two types of patient: (1) a group with a rather high urine calcium (mean about 0·25) who have failed to reduce it; and (2) a group, with a mean value obout 0·10, who have succeeded in reducing urine calcium but whose

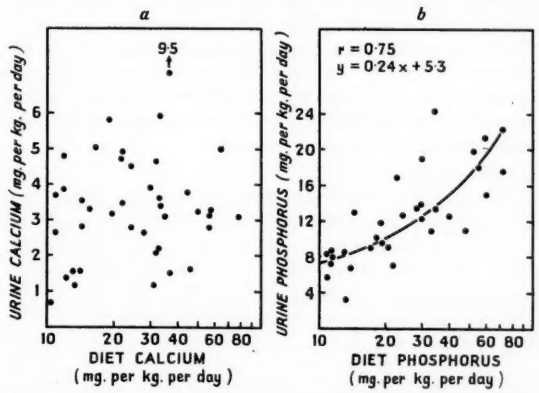

Fig. 5—(*a*) Urine calcium and dietary calcium in 40 balance studies on 20 cases of osteoporosis; (*b*) urine phosphorus and dietary phosphorus in 32 balance studies on 18 cases of osteoporosis.

intake or absorption is still inadequate. Further observations will be required to test this possibility.

These data suggest that, in osteoporosis, urine calcium is independent of calcium intake. This is supported by balance studies. Fig. 5a, based on 40 balance studies at

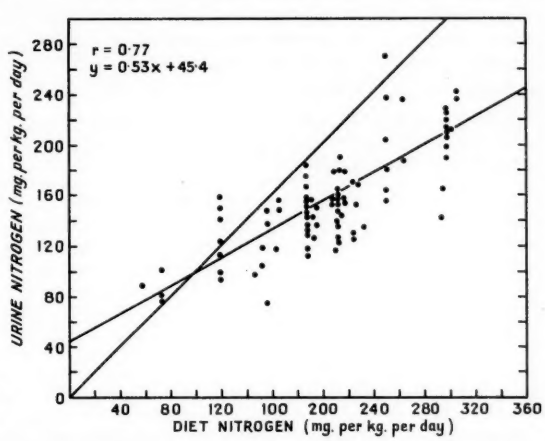

Fig. 6—Regression of urine nitrogen on dietary nitrogen in 84 balance periods on 17 cases of osteoporosis.

different levels of intake in 20 cases of osteoporosis, shows that urine calcium in these patients varies quite independently of calcium intake. By contrast, fig. 5b shows that urine phosphate in these same patients varies with phosphate intake. Thus, these patients adapt to a low phosphorus intake but not to a low calcium intake. Fig. 6 shows that these same patients vary their urine nitrogen in accordance with their intake. They are therefore unlikely to have been suffering from negative nitrogen balance due to dietary deficiency, nor have we yet

encountered negative nitrogen balance in any patient with primary osteoporosis studied on her home diet.

We have confirmed this abnormality of calcium excretion in yet another way. We have found that whereas in normal subjects, 10 days on a low calcium diet reduces urine calcium by at least 30%, little or no fall in urine calcium occurs in cases of osteoporosis. This is the only consistent biochemical abnormality to be found in this disease. It may, of course, be argued that this calcium " leak " is the result rather than the cause of the skeletal disorder, but it seems inherently more probable that the reverse is true. Just as menorrhagia is more likely to be the cause than the result of anæmia so is relative hypercalciuria more likely to be the cause than the result of osteoporosis.

Calcium Absorption

Calcium absorption can at present be determined only by balance studies. We have found that most patients with osteoporosis go into strongly positive balance when given calcium supplements (Nordin 1960c), thus confirming the findings of Owen et al. (1940), Whedon (1959), and Harrison and Fraser (personal communication). This suggests that malabsorption of calcium is not a major cause of osteoporosis. This is not true, however, of the patients with steatorrhœa, who constitute about 15% of our cases of osteoporosis. There are also a few patients without steatorrhœa who do not absorb well, and it is possible that some of these are suffering from a mild vitamin-D deficiency which interferes with calcium absorption, but is not sufficiently severe to produce osteomalacia. Osteomalacia is a well-recognised complication of steatorrhœa (Badenoch 1960), but osteoporosis is probably much commoner (Nordin 1961).

Calcium Therapy

In view of the balance results it seemed reasonable to study the effect of calcium supplements on backache. Table II shows the subjective response of 46 osteoporotic patients with backache of not less than one year's duration

TABLE III—SUBJECTIVE RESPONSE OF 46 PATIENTS WITH OSTEOPOROSIS TO THERAPY WITH CALCIUM GLYCEROPHOSPHATE 6 g. DAILY (≡1100 mg. of supplementary calcium)

Therapeutic response	Time (mos.)			
	1	3	6	12
A	0	1	14	22
B	3	24	16	14
C	21	10	5	2
D	17	10	11	8

A = pain free. C = possible improvement.
B = definite improvement. D = no change.

to long-term therapy with 6 g. of calcium glycerophosphate daily. With the passage of time an increasing proportion of patients appeared to respond, and 36 reported definite or complete relief of pain at the end of twelve months. (4 of the 11 patients who improved between the sixth and twelfth months were given small doses of vitamin D.) The 10 patients whose condition was more or less unchanged at the end of a year included 6 out of the 10 cases of peripheral osteoporosis in the series (Barnett and Nordin 1960). We have seen no convincing radiological improvement as a result of calcium therapy; only a possible hardening of the vertebral end-plates. On the other hand, only 2 patients have had further crush fractures while on this treatment.

Of the patients in whom calcium balances have been performed, those in the most strongly positive balance (more than 6 mg. per kg. per day) have generally shown the best response to long-term calcium therapy. That such apparently strongly positive calcium balance is required for the relief of symptoms might be due to the loss of calcium through the skin. This loss probably constitutes a systematic source of error in all balance work.

The rather delayed response to calcium therapy suggests that this is not a " placebo " effect; but, clearly, the further assessment of subjective improvement will require a controlled investigation (Wayne 1957). This is now in progress. The alleged efficiency of œstrogen therapy has been one of the main arguments for the " protein matrix " hypothesis: yet a recent trial did not confirm this general impression (Solomon et al. 1960).

Summary and Conclusions

I have outlined some of the considerations which suggest that primary osteoporosis could be due to long-continued negative calcium balance. This would cause the removal of mineral from bone followed at once by the removal of matrix (Carttar et al. 1950), thus reducing bone mass without reducing the mineral content of the residual bone.

This concept is strengthened by the recent histological observations of Jowsey (1960) and Sissons, Jowsey, and Stewart (1960) who find that the extent of the resorbing surface in the adult skeleton increases with advancing age without any corresponding increase in the bone-forming surface. This suggests that osteoporosis in the elderly is due to bone resorption. Only when bone destruction is very rapid and severe does it produce the picture of osteitis fibrosa, as it may do in hyperparathyroidism. On the other hand, osteoporosis and not osteitis fibrosa, may be the only bony manifestation of hyperparathyroidism (Cooke 1955). Osteitis fibrosa, however, may also be seen in hyperthyroidism, in which osteoporosis is the more usual bone lesion. These examples suggest that osteitis fibrosa and osteoporosis represent different degrees of an essentially similar process—e.g., bone resorption.

It must be emphasised that the low mineral content of rachitic or osteomalacic bone is not due to removal of mineral from bone but to failure of mineral deposition in young osteoid, leaving large uncalcified osteoid seams. For some reason unknown, uncalcified osteoid is left intact in the bone, whereas decalcified osteoid is quickly removed, possibly by osteoclasts. In this different behaviour of these two forms of osteoid lies an essential, perhaps the essential, difference between osteomalacia and osteoporosis.

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CALCIUM METABOLISM IN OSTEOPOROSIS

Acute and Long-term Responses to Increased Calcium Intake

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OSTEOPOROSIS, or atrophy of bone, was first described by Pommer in 1885. He distinguished it from osteomalacia, a condition in which defective calcification of the skeleton is shown by an excess of osteoid tissue, and which is often due to lack of vitamin D. Though osteoporosis is probably the commonest metabolic disorder affecting the skeleton in man, its cause remains a mystery. The disorder is characterised by uncomplicated skeletal atrophy; the bones are thin but otherwise normal structurally. The cause of the decreased amount of bone must therefore be either deficient bone formation, or excessive bone resorption, or both, though these processes remain qualitatively normal.

Earlier workers had suggested that calcium deficiency might be the cause of osteoporosis, but such a hypothesis was largely set aside when Albright et al. (1940) proposed that osteoporosis depended not on any abnormality of calcium metabolism, but on insufficiency of bone matrix due to defective osteoblastic activity. Only recently have tracer methods become available for measuring the rate of bone deposition or resorption (Bauer et al. 1957, Bauer and Ray 1958, Fraser et al. 1960) and, hence, for assessing the validity of this hypothesis. Because the results of these studies do not indicate a defect of bone formation in osteoporosis, and so are contrary to Albright's view, there is a clear need for appraisal of the role of calcium deficiency in producing this disorder.

We have therefore investigated the possibility that osteoporosis may result from calcium deficiency.

The Study

Plan of Study

It seemed likely that a patient with calcium deficiency would show an excessive avidity for calcium, and so would retain abnormally large amounts of calcium when the intake was high. Moreoever, this high retention should continue, if the high intake were continued, until the calcium deficiency was made good. On the other hand, in a patient with defective osteoblastic activity in the skeleton the opposite response would be expected—i.e., little avidity for calcium and a poor ability to continue to retain it. Calcium-balance studies have therefore been carried out to assess the basal calcium balance in osteoporotic patients, and their metabolic responses to increases, both short-term and long-term, of calcium intake.

To interpret the response to the acute increase of calcium intake the patients were investigated on a standard low-calcium diet, first with medium-calcium supplements and then with high-calcium supplements; and similar studies were also made on chosen normal and probably normal subjects. Thus each patient's balance—i.e., net absorption and urinary excretion of calcium—were measured on these two standard diets which differed only in their content of calcium. Then the patients continued on the high-calcium supplements after discharge; and at intervals further balance studies were made to determine whether a positive calcium balance still persisted. In some patients, androgens and œstrogens were given in addition, usually after a period on the high-calcium therapy alone.

Patients Studied

As far as possible, patients with uncomplicated postmenopausal or senile osteoporosis were chosen for study—i.e., 16 subjects over 60 or postmenopausal, with obvious osteoporosis, with or without fractures, but without any other clinically detectable complicating factor.

Comparable studies were also made on 8 chosen and 4 probably normal subjects, and on 6 patients with osteoporosis associated with other conditions. In this group, who were, in general, younger, 2 had postpartum osteoporosis, and in the 4 others the osteoporosis was associated with anorexia nervosa, immobilisation, Klinefelter's syndrome, or urticaria pigmentosa. In all the patients, other metabolic bone diseases had first been excluded by full biochemical and radiological investigations, and, where necessary, by a bone biopsy.

Calcium Content of Diets

The patients and normal subjects were balanced on different levels of calcium intake, in a standard sequence. The calcium intake was calculated according to body-weight. The first balance periods were carried out on a medium intake of 0·3 mEq. (6·7 mg.) calcium per kg. body-weight, and the second group of periods on a high intake of 2 mEq. (40 mg.) per kg. The lower intake represents about the lowest at which equilibrium can be achieved, without producing a negative calcium balance (Malm 1958), while the higher intake is the greatest which is practicable for long-term therapy. To allow greater accuracy in measurements of calcium intake, and also constancy of the other intakes, the same low-calcium diet was maintained throughout the balance periods (about 7·5 mEq. Ca per day); and the rest of the calcium intake was made up with tablets of calcium lactate (2 mEq. per tablet) or calcium gluconate Sandoz (19 mEq. per tablet). To prevent monotony, each patient received two diets which were alternated from day to day; these differed in composition but not in calcium content. Samples of these diets were analysed for calcium content, and and any rejections by the patient were weighed and allowed for in calculating the calcium intake.

Before commencing the balance, each patient was given the fixed calcium intake for three (or later five) days, in order to allow partial equilibration. Starting on the fourth (or, later, the sixth) day, two balance periods each of three days, were carried out, urine and fæces being separately pooled for each of the two periods. In every case the balances were first done while the patient was receiving the lower calcium intake. Then, usually immediately, or after an interval not greater than eleven days, the patient was allowed to equilibrate on the high-calcium intake for three to five days; this was followed by two more balance periods, each of three days, on the high-calcium intake.

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The balances were carried out in the metabolic ward of the Hammersmith Hospital. All patients were allowed normal activity as far as their general condition allowed, and none were confined to bed. Urine was collected in a winchester bottle containing 10 ml. concentrated hydrochloric acid, and fæcal specimens were collected directly in a large tin.

Estimation of Calcium

In urine.—1 ml. of acidified urine was added to phosphoric-acid/perchloric-acid mixture, and the calcium in the solution measured by the spectrophotometric method of MacIntyre (1957).

In fæces.—The three-day fæcal pool was homogenised by rolling the tin on mechanical rollers, with a cylindrical brass weight inside the tin. A portion of homogenised fæces was then dried under infra-red lamps, 1 g. was weighed into a crucible, dried again under the lamps after addition of a few drops of aqua regia (1 part concentrated nitric and 3 parts concentrated hydrochloric acids), ashed in a muffle furnace at 400°C for 18 hours, dried with the acid mixture, and ashed again. The ash was dissolved in concentrated hydrochloric acid, and the solution was made up to a known volume with distilled water. The calcium content of the solution was measured on the flame spectrophotometer.

In diet.—Weighed samples of each diet were blended in an electric mixer. 1 g. portions of the blended sample were treated as described for the fæcal pools, and their calcium content measured.

Calculation of True Fæcal Calcium

Some allowance has to be made for variations in fæcal calcium output over the three-day collections, because the actual output collected does not necessarily represent accurately the intestinal excretion of calcium over this time, owing to variations in the extent of transfer of the intestinal contents at each bowel movement. In the earlier balances of this series a rough correction was made with fæcal nitrogen. The calcium output over each three-day period was corrected for the mean fæcal nitrogen excretion over the two periods; since, on a given protein intake, fæcal nitrogen is constant from day to day (Reifenstein et al. 1945). If, after correction, the two fæcal calcium pools did not agree to within 30%, they were regarded as invalid, and were not included in the series.

Subsequently, we studied the fate of orally administered chromium sesquioxide, Cr_2O_3, in rats and in man, to demonstrate that none is absorbed. In the investigations with rats, Cr_2O_3 labelled with ^{51}Cr was administered to the animals in a gelatin capsule, introduced into the stomach through a small tube. The rats were then placed in metabolism cages and their excreta collected for the next three days. All the ingested ^{51}Cr was fully recovered in the excreta. Similar findings were obtained in man, with stable Cr_2O_3. Details of the method of estimation and the use of Cr_2O_3 in balance studies have been published (Whitby and Lang 1960); as illustrated by our data, the accuracy of our measurement of fæcal excretion of calcium was clearly enhanced in this way.

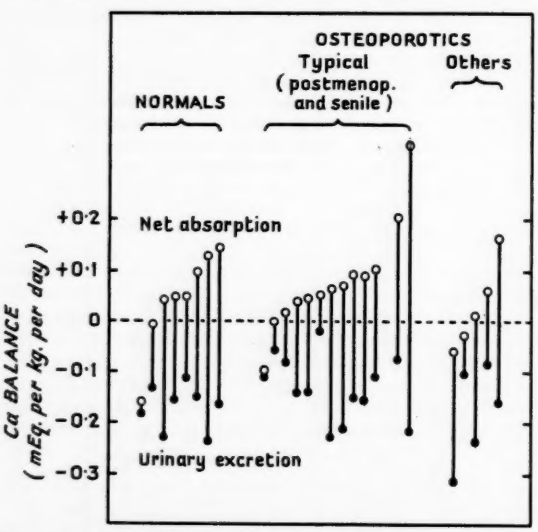

Fig. 1—Calcium balances in normals, postmenopausal or senile osteoporotics, and miscellaneous osteoporotic subjects on a medium-calcium intake (0·33 mEq. per kg. per day).
There are no differences between the groups.

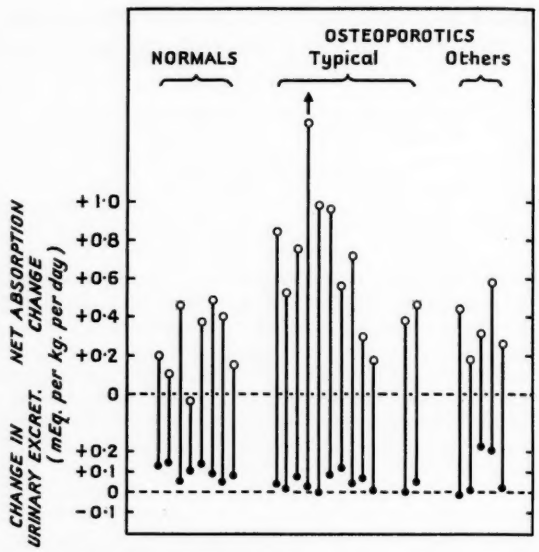

Fig. 2—Change in net absorption and urinary calcium immediately after the establishment of a high-calcium intake (2 mEq. per kg. per day) preceded by a medium-calcium intake (0·33 mEq. per kg. per day).
There was excessive increase in net absorption in 8 of the 12 postmenopausal and in 1 of the 5 "atypical" osteoporotics, compared with the normals.

Results

Basal Calcium Balance on Medium-calcium Intake (0·3 mEq. per kg. per day)

Fig. 1 shows that on the medium-calcium intake the osteoporotic patients appear to handle calcium normally; both net absorption (calcium intake minus fæcal calcium) and urinary excretion are normal. The level of blood-calcium is also normal in osteoporosis, and we have already reported that the rate of bone deposition of calcium on this same intake is normal in this condition (Fraser et al. 1960). All these findings are in agreement with those of other workers (Albright and Reifenstein 1948, Nordin 1959, Heaney and Whedon 1958) and indicate that on a medium or low calcium intake no abnormality of calcium metabolism is found in osteoporosis.

Changes in Calcium Balance immediately after Transfer to High-calcium Intake (2 mEq. per kg. per day)

Fig. 2 shows the changes in calcium balance observed immediately after transferring the subjects from the medium to the high calcium intake. In the normal controls there was a slight increase in urinary calcium loss (mean +0·090: range +0·027 to +0·145 mEq. per kg. per day), and a moderate increase in net absorption (mean +0·269: range −0·019 to +0·489 mEq. per kg. per day). But, as a group, the patients with postmenopausal and senile osteoporosis have shown a different metabolic response to

this dietary increase—i.e., possibly less increase of urinary calcium loss (mean +0·043: range −0·001 to +0·115 mEq. per kg. per day) and considerably greater increase in net absorption of calcium (mean +0·701: range +0·132 to +1·905 mEq. per kg. per day). Fig. 3 shows that their calcium balance has usually become more strongly positive on moving to the high-calcium intake than has that of the normals—their mean calcium balance on the high intake being +0·626 (range −0·072 to +1·913) as against the normal mean of +0·091 (range −0·235 to +0·351 mEq. per kg. per day). These changes suggest, as does also the increased absorption of calcium, a response at the bone surface to this dietary increase—less bone resorption or more deposition of calcium, or both. They also show that these changes are greater in the osteoporotic patients than in the normal subjects. In some of the patients, however, the response was not different from that of the normals; this was the case in 4 of the 12 postmenopausal and senile osteoporotic patients,

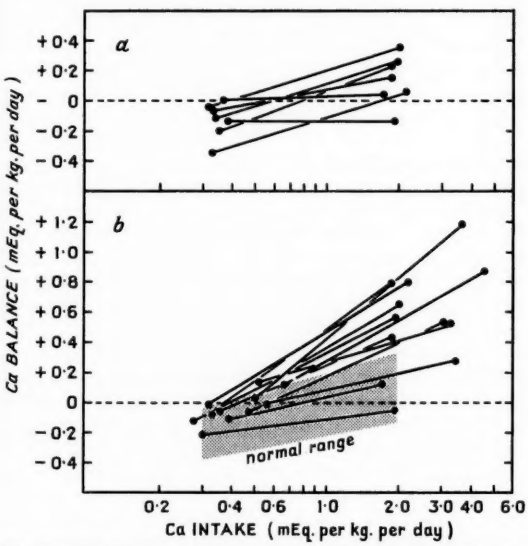

Fig. 3—Total external calcium balance in (*a*) normal and (*b*) osteoporotic subjects, first on a medium-calcium intake (0·33 mEq. per kg. per day) and then immediately after instituting a high-calcium intake (2 mEq. per kg. per day).

On changing to a high-calcium diet, the normals have a moderately positive calcium balance, but most of the osteoporotics show a more strongly positive calcium balance.

and in 4 of the 5 younger or "atypical" osteoporotic patients.

Persistence of the Positive Calcium Balance in Osteoporotic Patients on a High-calcium Intake

In several patients the balance has been rechecked after about nine months on a high-calcium intake; in some it has also been rechecked on several occasions, and after longer periods of up to three and a half years. Figs. 4 and 5 show the data at present available. They indicate that a strongly positive calcium balance can be maintained in many (4 out of 6) of the postmenopausal and senile osteoporotic patients for at least one to three years.

After the second, or a later reassessment, of calcium balance, androgen and œstrogen therapy* has been given

* 'Primodian-Depot' 1 ml. per month intramuscularly has been used; 1 ml. contains 65 mg. testosterone œnanthate and 4 mg. of œstradiol valerianate.

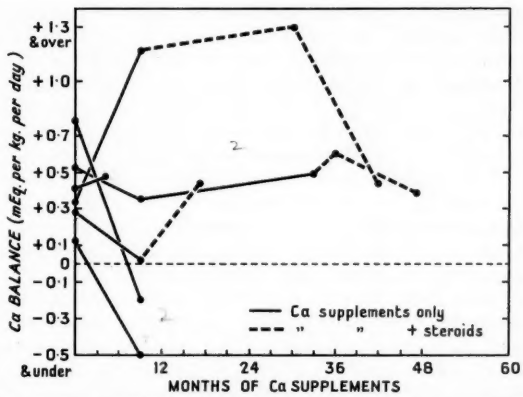

Fig. 4—The persistence in postmenopausal and senile osteoporotics of a positive calcium balance on a high (2 mEq. per kg. per day) intake.

A positive calcium balance was maintained longer in 4 of the 6 subjects having calcium supplements.

in addition to the high-calcium intake to some of the patients. There are not enough data to assess whether there is any additional effect from these hormones, but the long-lasting positive calcium balance is evident, with or without added hormones. Among 3 of the younger patients with osteroporosis studied, no similar tendency to long-continued calcium retention was found—after a prolonged high-calcium intake the balance was negative or only slightly positive.

In the postmenopausal and senile group, long-term treatment with calcium supplements seemed to relieve the bone pain, whenever it had been present, and there have been no new fractures; but we still are assessing whether any correction of the osteoporosis becomes demonstrable radiologically.

Discussion

These studies demonstrate an abnormality of calcium metabolism in over half of the patients with postmenopausal and senile osteoporosis—namely, an excessive and persisting avidity for calcium when large calcium supplements are given. This abnormality has not been found in all this group of patients, possibly because some of the patients were at a different stage of the disease or had another form of osteoporosis. This point has yet to be settled; but, as the abnormality is demonstrable in the majority of patients, hypotheses of the cause of osteo-

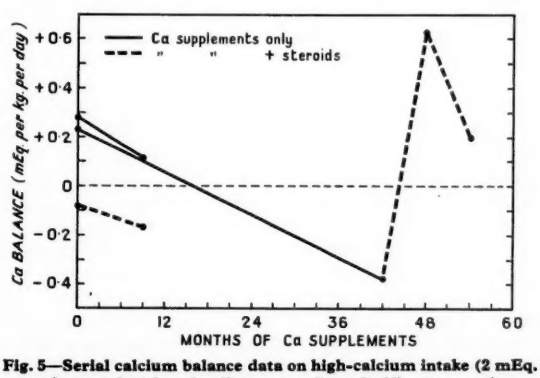

Fig. 5—Serial calcium balance data on high-calcium intake (2 mEq. per kg. per day) in miscellaneous or "atypical" osteoporotics.

In contrast with fig. 4, there is little tendency to long-continued strongly positive calcium balance.

porosis and its therapy should take account of this metabolic feature. As far as they could be assessed, our patients were typical—any with unusual features, such as associated anorexia nervosa, having been relegated to the "atypical" group. A few of our patients had the high urinary excretion of calcium which is sometimes seen in osteoporosis, but they showed no other unusual features.

These patients show no abnormality of calcium balance on medium or on low calcium intakes (Albright and Reifenstein 1948) nor any abnormality of serum-calcium level, nor of the rate of calcium deposition in bone as measured by tracer tests (Heaney and Whedon 1958, Nordin 1959, Fraser et al. 1960). On a high-calcium intake, however, they show an avidity for calcium—i.e., both an increased efficiency of calcium absorption and an increased retention of calcium in the body, presumably in bone. Not only does the calcium balance show this excessive retention when a high intake is first given, but, with several patients, we have found that the high retention is maintained for up to three and a half years.

A similar avidity for calcium was observed by Bauer and Marble (1932) and by Adams et al. (1936) in single osteoporotic subjects whose previous diet had clearly been deficient in calcium; and also by Morris et al. (1943) in several osteoporotic patients. Balance studies to observe the effects of œstrogens in postmenopausal osteoporotic patients have usually been based on either a medium-calcium or a high-calcium intake achieved by altering the diet rather than by giving calcium supplements, with the result that the phosphorus intake was also correspondingly raised (Albright and Reifenstein 1948, Anderson 1950). The patient's avidity for calcium may be obscured when the phosphorus intake is also high, because the latter tends to increase the fæcal loss of calcium. Moreover, these workers have not offered for comparison similar balance data from normal subjects. Whedon (1959) and Nordin (1960a) have also noted some persisting positive calcium balances when osteoporotic patients were given calcium supplements, and others have reported clinical benefit from such therapy.

Hitherto it has been notoriously difficult (Henneman and Wallach 1957) to obtain sufficient improvement in the osteroporosis with the conventional androgen-œstrogen treatment, and this may well reflect the resistance of the disease to any therapy. Hence, a long period of treatment with calcium supplements may be needed to assess their full therapeutic potentialities.

In patients showing avidity for calcium, it is difficult to accept the hypothesis that their osteoporosis depends on defective osteoblastic activity. The simplest explanation of the avidity would be that it reflects a previous calcium deficiency, and this could well be the whole cause of the osteoporosis. Retrospective assessments of the dietary intake of a group of osteoporotic patients have found them subnormal in calcium and protein content, but not in vitamin D (Nordin 1960b). Further, by comparing published dietary surveys with the estimates of calcium requirement obtained from balance studies on normal subjects, Nordin (1960b) found that the calcium intake of a fair proportion of the British population may be less than they require to maintain calcium balance. Though the commonly advocated calcium requirement of 800 mg. per day is above the mean total calcium excretion found in normal balance studies, there is a wide, largely independent, individual variation in both intake and total excretion. Pett (1955) concluded from a study of balance data that this recommended requirement was adequate, but he did not consider balances throughout the range of normal intakes. Malm (1958) in careful long-term balances on prisoners found that 8% were in negative balance on a calcium intake of 940 mg. per day, though they appeared healthy. Among the 38 of his sample of men X-rayed, 10 showed some thinning of the bones, and he found that their previous calcium and vitamin-D intake had been inadequate. There are earlier scattered observations of an inadequate intake of calcium among patients with osteoporosis (reviewed by Nordin 1960a), and benefit has been claimed from therapy with calcium supplements.

Animal investigations have established that a severe calcium deficiency, leading to chronic negative calcium balance, causes osteoporosis (e.g., Crawford et al. 1957, Greaves et al. 1959, Scott 1960, Harrison and Fraser 1960). Harrison and Fraser (1960) have shown that the rate of bone deposition of calcium in this type of osteoporosis, far from being decreased, is abnormally rapid. Only when there is vitamin-D deficiency in addition to calcium deficiency does osteomalacia also develop (Crawford et al 1957, Harrison and Fraser 1960). Nicolaysen (1956) has shown that rats on a low-calcium intake tend to increase their absorptive efficiency provided they are not deficient in vitamin D; and Malm (1958) has found this adaptation in man, but the efficiency of it varies considerably. Such a variation in adaptation to low-calcium intake may explain why many races—e.g., Chinese, Indians, and Bantus—remain healthy on calcium intakes less than 500 mg. per day, though Europeans may develop osteoporosis on a high-calcium intake. The physiological basis of this adaptation may involve such factors as vitamin-D intake and exercise, but has not been elucidated. Calcium-deficient animals, especially when young, have skeletons avid for calcium, but this avidity declines with age (Harrison and Fraser 1960). Thus, age tends to exacerbate the osteoporosis of calcium deficiency and to obscure the avidity for calcium which might reveal its basis. In such animals with osteoporosis due to calcium deficiency the parathyroid glands are enlarged, and after an early parathyroidectomy the osteoporosis is not so severe (Harrison and Fraser 1960). Evidently secondary hyperparathyroidism and consequent excessive bone resorption develop when calcium intake is inadequate, to maintain normal serum-calcium levels. In the patients with osteoporosis, a high-calcium intake probably leads to excessive retention of calcium by suppressing this secondary hyperparathyroidism, and therefore arresting the rapid bone resorption. An alteration of the rate of bone formation seems less likely.

Clearly, if osteoporosis arises from calcium deficiency, it may result not only from lack of dietary calcium but from any factors which cause a negative calcium balance; hence in some instances it may result from an increased rate of bone resorption and/or of urinary or fæcal calcium loss. Defective skeletal matrix may also be a factor in some cases, such as osteogenesis imperfecta and corticosteroid-induced osteoporosis. To cure osteoporosis not only must a negative calcium balance be reversed but also a large amount of new bone must be deposited; and many factors, including age, may handicap the successful treatment of osteoporotic patients by calcium supplements. The response to treatment is likely to be slow, and sometimes the condition may only be arrested and not reversed. Longer periods of observation are needed to assess the efficacy of this treatment of osteoporotic patients with calcium supplements, for which these balance studies offer the indication.

Summary

The cause of osteoporosis, or "simple" atrophy of bone, is not known. Recent studies of calcium metabolism

do not support the widely accepted hypothesis that osteoporosis results from defective osteoblastic activity. Studies are reported here which suggest that calcium deficiency is an important factor in many cases of post-menopausal and senile osteoporosis. Many patients with these forms of osteoporosis absorb and retain calcium abnormally avidly when on a high-calcium intake in the form of supplements (calcium gluconate Sandoz), and moreover may continue to retain it avidly for at least three and a half years. Symptoms of the disease are relieved, and no further fractures take place. Therapy with calcium supplements, therefore, seems to be of value for many patients with osteoporosis.

We should like to thank Dr. Iain MacIntyre and the other members of the staff of the department of chemical pathology who carried out some of the chemical estimations for these balance studies; and the dieticians, sister, and staff of the metabolic ward, Hammersmith Hospital, who supervised the balance regimen. We are grateful to Messrs. Sandoz for the supply of calcium gluconate tablets, and to the Schering A.G., Berlin, for 'Primodian-Depot' injections.

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LIPID PATTERNS IN MYOCARDIAL INFARCTION AND ANGINA PECTORIS

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IN 1951 Morris published evidence that over the years 1907–49 myocardial infarction had become more common, whereas the prevalence of coronary-artery disease, as judged by coronary calcification, had decreased. Later, Morris et al. (1953) showed that a sedentary occupation carries a greater risk of myocardial infarction; and, in particular, when ischæmic heart-disease develops that bus-drivers tend to have myocardial infarction and conductors angina pectoris. This suggests that ischæmic heart-disease comprises two subgroups of different pathogenesis—namely, myocardial infarction and angina pectoris.

TABLE II—SERUM-LIPOPROTEINS IN ANGINA PECTORIS (Lyon et al. 1956)

Group	Standard Sf 0–12 (mg. per 100 ml.)	Standard Sf 12–400 (mg. per 100 ml.)
Angina pectoris becoming infarctions (31 cases)	422·4	354·8
Angina pectoris remaining uncomplicated (88 cases)	410·5	259·4
Difference	11·9	95·4

In a therapeutic trial over the past three years, we have studied patients with ischæmic heart-disease; and repeated lipid examinations have been performed. We here present our results, showing that the serum-lipid patterns differ in myocardial infarction and angina pectoris.

Methods

Male patients were studied up to the age of sixty-five: Patients were considered to have *myocardial infarction* when (1) the electrocardiogram (E.C.G.) showed typical changes with pathological Q waves (most of these patients had a typical history of rest pain and had been treated in hospital), or (2) they had a typical history of angina at rest lasting for more than an hour and accompanied by major ST changes without Q waves, and with raised transaminase levels. There were 46 such patients. Serum-lipid examinations were not performed until eight weeks after the myocardial infarction.

Patients were classified as having *angina pectoris* if they had angina of effort and E.C.G. changes at rest or exertion, without pathological Q waves. This group consisted of 48 patients.

All patients were randomly allocated to treatment with (1) a diet low in saturated and high in unsaturated fats, or (2) long-term phenindione. They were seen at three-monthly intervals for clinical, E.C.G., and serum-lipid examinations. The diet resulted in striking lowering of lipid levels of the blood, and only one or two representative lipid estimations are available in those treated in this way. The patients who were given only anticoagulants, however, had lipid examinations on many occasions for a three-year period, and all their results were used in our analysis.

Total-serum-cholesterol levels were estimated by the method of Abell et al. (1952), and low-density lipoproteins by the method of Lindgren and Gofman (1957).

Results

Table I shows the results.

The patients with myocardial infarction were similar to those with angina pectoris in age, height, and weight. The mean total-serum-cholesterol level was 10 mg. higher in the myocardial-infarct group, but this amounts to only 3·5%, and is not significant at the 5% level.

The mean level of low-density lipoproteins of patients with myocardial infarction is higher by 111 mg. per 100 ml. (nearly 15%), and the difference in Sf 12–400 is 92 mg. (more than 32%), these differences both being significant at less than the 1% level. Sf 0–12 is 32 mg. per 100 ml. higher in the infarct group, a difference of 7%, and this is significant at the 5% level.

TABLE I—MEAN SERUM-LIPID LEVELS (mg. per 100 ml. ± S.E.)

—	Cholesterol	Low-density lipoprotein	Sf 0–12	Sf 12–400	Age (yr.)	Weight (lb.)	Height (in.)
Myocardial infarction (46 patients—95 observations)	301 ± 4·1	858 ± 18·5	488 ± 9·1	374 ± 12·9	53 ± 1·2	163 ± 1·6	67 ± ·9
Angina pectoris (48 patients—100 observations)	291 ± 4·1	747 ± 15·6	456 ± 8·8	282 ± 11·7	54 ± 1·5	161 ± 1·6	67 ± ·72
Difference	10	111	32	92	1	2	..
	0·1 > P > 0·05	P < 0·001	0·5 > P > 0·02	P < 0·001	N.S.	N.S.	

N.S. = not significant.

Discussion

Our data show a considerable difference between patients who have had myocardial infarction and those with angina. The levels of all the lipid fractions examined were higher in the myocardial-infarction group, but strikingly so only in lipoproteins Sf 12–400.

Similar data to ours can be found in a paper by Lawry et al. (1957), but they do not comment on these facts. Lyon et al. (1956) compared patients with angina pectoris who later developed myocardial infarction with those who did not; the lipid levels of their series, shown in table II, agree closely with ours. Unfortunately, they do not include serum-cholesterol levels. Kagan (1960) showed that bus-drivers, who are prone to myocardial infarction, have higher levels of Sf 20–400 than conductors, who tend to get angina pectoris.

The largest amount of serum-cholesterol is carried in lipoprotein Sf 0–12, whereas lipoprotein Sf 12–400 contains the major proportion of triglyceride; comparison between serum levels of cholesterol and triglyceride should therefore be pertinent. Antonis and Bersohn (1960) showed that patients with myocardial infarction have raised levels of serum-triglyceride compared with normal control subjects, but they did not study patients with angina pectoris. The data of Schrade et al. (1960) showed that patients with myocardial infarction had somewhat higher levels of serum-triglyceride than had patients with angina pectoris, whereas the serum-cholesterol levels were almost equal in the two groups.

We conclude, therefore, that the rise of serum lipids in myocardial infarction is not only quantitatively higher but also qualitatively different; and, since the different lipid fractions are influenced by different metabolic processes, this may have pathogenic significance.

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RED-CELL FRAGMENTATION SYNDROME

A Condition of Multiple Ætiology?

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SEVEN fatal cases of hæmolytic anæmia, thrombocytopenia, and oliguria in children were described by Gasser et al. in 1955. In all patients they found bizarrely fragmented red blood-cells in the peripheral blood-film, and at necropsy bilateral renal cortical necrosis of varying extent. Allison (1957) reported six further examples of the syndrome, all in children, two of whom died; in these necropsy showed no renal cortical necrosis but widespread platelet thrombi. He concluded that the condition was a form of thrombotic thrombocytopenia. At this hospital we have seen five cases in the past eighteen months; but both clinical and necropsy evidence point to a variety of underlying pathological processes.

Case-reports

Case 1.—A 5-month-old boy was admitted to another hospital with a two-day history of diarrhœa, vomiting, drowsiness, and frequent generalised twitching. He was anæmic with a hæmoglobin (Hb) of 5·8 g. per 100 ml. (40%). The urine contained 3 g. of protein per 100 ml., no white blood-cells (W.B.C.), and only a few red blood-cells (R.B.C.). Shortly after his admission extreme oliguria developed, and he was found to have a low serum-sodium and a high serum-potassium. After transfusion with 250 ml. packed cells the hæmoglobin rose to 11·1 g. per 100 ml. (76%), but the low urinary output persisted. He was transferred to the Hospital for Sick Children for further investigation.

Examination and investigations.—The patient was pale and fretful with slight œdema in the lower limbs. The kidneys and bladder were not palpable. The Hb was 8·9 g. per 100 ml. (61%), reticulocytes 13%, and W.B.C. 8300 per c.mm. with a normal differential count. The stained film (fig. 1) showed considerable anisocytosis, poikilocytosis, bizarrely shaped red cells—including many "triangular" and "burr" forms—and considerable polychromasia. No Heinz-bodies were seen. The platelet-count was 77,000 per c.mm. The direct Coombs test was negative and red-cell osmotic fragility was normal. Plasma-electrolytes (mEq. per litre) were: sodium 129, potassium 5·3, chloride 91, bicarbonate 16. The blood-urea was 220 mg. per 100 ml.

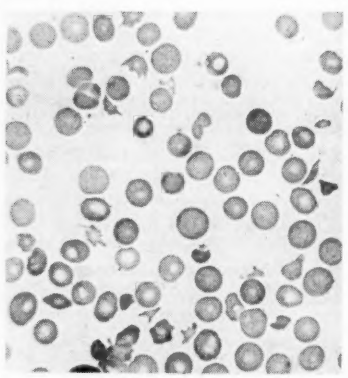

Fig. 1—Case 1: stained blood-film.

Course.—The patient's fluid intake was restricted and he started to pass small amounts of urine; but his blood-urea continued to rise, and the electrolyte imbalance persisted. Two days after admission his hæmoglobin was 7·5 g. per 100 ml. (51%), and in the stained film the platelets were still very scanty. The next day right-sided pneumonia developed, and his hæmoglobin was 5·3 g. (36%). Despite a small blood-transfusion he collapsed and died that evening.

Necropsy (Dr. Martin Bodian).—The *lungs* showed pulmonary œdema and multiple areas of hæmorrhagic consolidation in all lobes. The *kidneys* weighed 38 g. (right) and 44 g. (left) (normal 25 g. each) and showed the typical naked-eye and histological changes of acute glomerulonephritis.

Case 2.—A boy with congenital spherocytosis was clinically cured by splenectomy at the age of 4 months. Some months later an upper-respiratory-tract infection developed; at first this responded well to penicillin, but three weeks later otorrhœa, diarrhœa, and vomiting developed. The patient was admitted extremely ill to another hospital, where slight neck rigidity and a petechial rash suggested the diagnosis of meningococcal septicæmia. The cerebrospinal fluid, however, was normal. He improved on antibiotics and prednisolone, but his hæmoglobin, which had been 9·6 g. per 100 ml. (66%) on admission, fell to 6·0 g. three days later. He was transfused with 1 pint of blood, but his hæmoglobin fell again and the percentage of reticulocytes rose. The platelet-count, which had

been normal on his previous admission for splenectomy, was now consistently in the region of 50,000 per c.mm. He was transferred to the Hospital for Sick Children ten days after admission.

Examination.—The patient was very ill, cyanosed, and dyspnoeic, with a temperature of 101° F, and bruising and purpura on both legs. The ears were not inflamed but he had bilateral bronchitis. The liver edge could be felt $1^1/_2$ in. below the costal margin, but the spleen and kidneys were not palpable.

Investigations.—Hb 8·5 g. per 100 ml. (58%) W.B.C. 16,600 per c.mm. (neutrophils 60%, lymphocytes 38%, monocytes 2%); 27 normoblasts per 100 W.B.C.; reticulocytes 10%. The platelet-count was 27,000 per c.mm. The blood-film showed a moderate number of spherocytes, considerable anisocytosis, poikilocytosis, and polychromasia, and many "burr and "triangular" forms of red cells. No Heinz-bodies were seen. The direct Coombs test was negative, and the red-cell osmotic fragility was normal. Plasma-electrolytes (mEq. per litre): sodium 135, potassium 5·4, chloride 90; total carbon dioxide 5 millimoles per litre. Blood-urea 630 mg. per 100 ml. Throat swab and blood-culture yielded no growth. The urine left no deposit and was sterile on culture, but it contained 200 mg. of protein per 100 ml.

Course.—The child became oliguric shortly after admission, and, despite an intragastric drip of fat and glucose, with small volumes of *M*/6 sodium lactate intravenously, his condition slowly deteriorated and he died four days later.

Necropsy (Dr. Martin Bodian).—*The middle ears and mastoids* were clear. The *brain* was œdematous, and there was a small subdural hæmatoma in the right posterior parietal region. The *meninges* were not inflamed. Both *lungs* were very œdematous, and the right showed a large zone of hæmorrhagic consolidation. The *kidneys* weighed 40 g. (right), 47 g. (left). The capsules stripped readily and were under tension. The cortical surfaces showed pale irregular areas with hæmorrhagic margins, and on section intensely congested outer zones and pale inner zones could be distinguished. The medullary pyramids were congested but not necrosed, and the medullary papillæ were firm and normal. Histologically the findings were those of extensive cortical necrosis with widespread hyaline thrombi.

Case 3.—A month-old boy was admitted to another hospital with continuous convulsions. Both kidneys were palpable and the urine contained a moderate number of casts and many pus cells and grew a paracolon bacillus and proteus. The blood-urea was 180 mg. per 100 ml. On antibiotics his condition improved, but intravenous pyelography failed to show excretion in either kidney.

Examination and investigations.—On admission to this hospital the child was fit but pale; the kidneys were no longer palpable. The blood-urea and serum-potassium were still raised. Other investigations showed: Hb 6·1 g. per 100 ml. (42%); W.B.C. 21,000 per c.mm. (neutrophils 48%, lymphocytes 45%, monocytes 5%, myelocytes 2%); 10 normoblasts per 100 W.B.C. In the stained film considerable anisocytosis and poikilocytosis, with numerous "burr" and "triangular" cells, and moderate polychromasia were seen, and the platelets were scanty. The platelet-count was 110,000 per c.mm. Heinz-bodies were not seen, and the direct Coombs test was negative. The red-cell fragility was normal.

Course.—A blood-transfusion raised the hæmoglobin to 17 g. per 100 ml., and thereafter the child did very well—although the platelet-count remained between 85,000 and 90,000 per c.mm. The blood-urea fell rapidly, and repeat intravenous pyelography showed normal excretion in both kidneys. The patient was discharged and he has remained well for nine months. Platelet-counts as an outpatient have been normal.

Case 4.—A 6-month-old girl, who had previously been well, was admitted to another hospital with a three-day history of diarrhœa and vomiting. She was febrile, listless, and

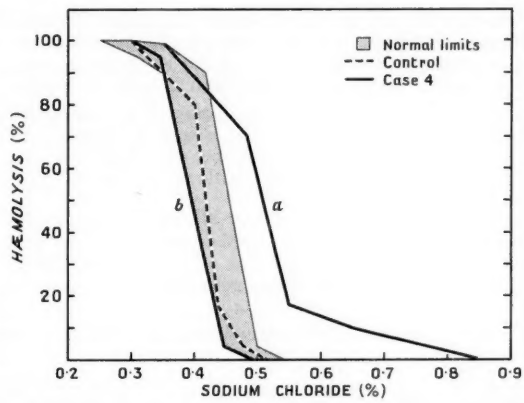

Fig. 2—Case 4: red-cell osmotic fragility in saline solution at 20°C (*a*) at beginning of illness, and (*b*) after recovery.

clinically severely anæmic. Three hours after admission bruises developed on both thighs, and scattered purpuric spots were noted on the trunk and limbs. She had no other abnormal physical signs. The Hb was 5·1 g. per 100 ml. (35%), and the blood-film showed anisocytosis and poikilocytosis with many cell fragments. The urine contained much albumin but no casts, and it was sterile. The cerebrospinal fluid was normal, and the blood-culture was sterile. The patient was treated with antibiotics and sulphonamides and transfused with 150 ml. blood. The blood-urea two days after admission was 220 mg. per 100 ml. Despite transfusion the hæmoglobin fell rapidly and normoblasts appeared in the blood-film; the blood-urea remained high. She was transferred to the Hospital for Sick Children with a provisional diagnosis of renal-vein thrombosis and hæmolytic anæmia.

Examination and investigations.—On admission the patient was very pale and ill but had no bruising or petechiæ. Both liver and spleen were palpable just below the costal margin, but the kidneys were not felt. Hb 5·1 g. per 100 ml. (35%); W.B.C. 9400 per c.mm. (differential count normal); 20 normoblasts per 100 W.B.C.; reticulocyte-count 19%; platelet-count 104,000 per c.mm. The blood-film showed gross anisocytosis and poikilocytosis with numerous "triangular" cells and microspherocytes and occasional "burr" cells. The direct Coombs test was negative. The red-cell fragility was greatly increased (fig. 2). The serum-bilirubin was 1·4 mg. per 100 ml., and the serum-electrolytes (mEq. per litre) were: sodium 148, potassium 4·5, chloride 107, bicarbonate 29. The blood-urea was 222 mg. per 100 ml.

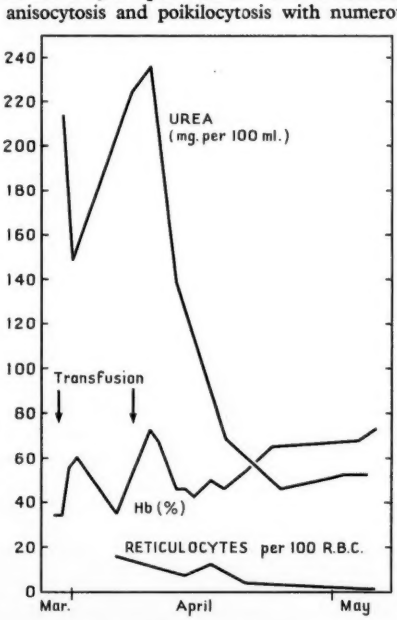

Fig. 3—Progress in case 4.

Course.—The patient's progress is

summarised in fig. 3. The spleen became impalpable a week after admission. At discharge five weeks later she was very well and had gained weight on a full diet. Red-cell fragility at this time was normal (fig. 2), and she has remained well for eighteen months.

Case 5.—A 5-month-old girl was admitted to the Hospital for Sick Children with a three-day history of diarrhœa and vomiting. She was pale and irritable, but not dehydrated. The liver was palpable just below the costal margin, but the spleen was not felt.

Investigations.—Hb 5·3 g. per 100 ml. (36%); W.B.C. 16,200 per c.mm. (neutrophils 43%, lymphocytes 52%, monocytes 5%); 4 normoblasts per 100 W.B.C. Blood-film showed occasional " burr " cells and numerous microspherocytes and " triangular " cells, gross anisocytosis, and considerable polychromasia. The platelet-count was 124,000 per c.mm. The direct Coombs test was negative. No Heinz bodies were seen. Serum-electrolytes (mEq. per litre): sodium 137, potassium 7·4, chloride 84, bicarbonate 11. Blood-urea 365 mg. per 100 ml. Cerebrospinal fluid normal.

Course.—On the day following admission the platelet-count was 50,000 per c.mm. Because the patient's condition deteriorated rapidly and she passed no urine after the evening of admission, she was transferred to Hammersmith Hospital for treatment by the artificial kidney. Renal dialysis with transfusion of packed cells was performed twice with reasonable clearance of urea and correction of the electrolyte imbalance;

CLINICAL AND PATHOLOGICAL FEATURES OF REPORTED CASES OF RED-CELL FRAGMENTATION SYNDROME

Author and case no.	Age	Sex	Clinical features	Apparent ætiology	Initial Hb (g. per 100 ml.)	Reticulocytes (%)	Platelets (per c.mm.)	Coombs test	Red-cell osmotic fragility	Blood-urea (mg. per 100 ml.)	Urine
Gasser et al. (1955):											
1	7 yr.	F	Subacute hæmolytic anæmia, jaundice, anuria; death	Bilateral renal cortical necrosis	5·8	2 (later 15)	45,000	Neg.	Normal	100*	Protein ++, casts ++, blood +
2	2 mo.	F	Upper resp. tract infection, cramps, hæmoglobinuria, anuria; death	Do.	3·8	..	Low on film	Neg.	..	Raised	Protein ++, casts +
3	7 mo.	F	Pallor, jaundice, hæmoglobinuria, hemiparesis, anuria; death	Do., secondary to thrombo-microangiopathy	5·5	8 (later 35)	79,000	Neg.	Raised	55*	Protein ++, casts +
4	13 mo.	F	Acute otitis, pneumonia, cramps, anuria, hæmoglobinuria; death	Bilateral renal cortical necrosis	Normal initially, then low	..	Low on film	Neg.	..	Raised	Blood +
5	14 mo.	M	Pneumonia, cramps, anuria; death	Do.	2·4	6·1	Do.	++	..	..	..
Allison (1957):											
1	2 mo.	F	Vomiting, jaundice, anuria; death	Widespread platelet thrombi	7	4 (later 10)	Do.	Neg.	..	..	Protein +
2	6 mo.	M	Diarrhœa, convulsions, anuria; death	Do.	7·1	6	..	..	..	300	Protein ++, blood ++
3	7 mo.	M	Pallor, anorexia, vomiting, hepatosplenomegaly; recovery after 14 days	?	4·9	25	20,000	Neg.	..	125	Protein ++, casts +, blood +
4	6 mo.	M	Sore throat, nasal discharge, pallor, vomiting, hepatomegaly; recovery after 7 days	?	6·7	Much polychromasia on film	Low on film	Neg.	..	53	Protein +
5	7 mo.	M	Bronchitis, hepatosplenomegaly, jaundice, vomiting; recovery after 7 days	?	6	32	Do.	Neg.	Normal but some resistant cells	..	Protein +
6	1 mo.	F	Jaundice, pallor; recovery after 7 days	?	8·1 (later 7)	17 (later 28)	Do.	Neg.	Do.	70	..
Aherne (1957):											
1	10 yr.	F	Sore throat, nasal discharge, vomiting; recovery after 3 days	?	10·4 (later 9·3)	8	92,000 (later 47,000)	Neg.	Normal	106	Protein +
Present series:											
1	5 mo.	M	Diarrhœa, vomiting, drowsiness, oliguria, pneumonia; death	Acute glomerulonephritis	5·8	13	45,000	Neg.	Do.	220	Protein ++
2	8 mo.	M	Otorrhœa, diarrhœa, vomiting, hepatomegaly, oliguria; death	Bilateral renal cortical necrosis	9·6 (later 6·0)	10	27,000	Neg.	Do.	630	Protein +
3	1 mo.	M	Those of renal infection and convulsions; recovery after 10 days	Renal infection	6·1	Moderate polychromasia on film	110,000 (later 85,000)	Neg.	Do.	180	Protein +, pus cells, proteus
4	6 mo.	F	Diarrhœa, vomiting, pallor; recovery	?	5·1	19	104,000	Neg.	Raised	222	Protein +
5	5 mo.	F	Diarrhœa, vomiting, pallor, hepatomegaly, oliguria; death	?	5·3	Considerable polychromasia on film	50,000	Neg.	..	365	..

* These values are for non-protein nitrogen.

The case reported by Shumway and Miller (1957) has not been included, because several of its features were unusual.

but her condition deteriorated still further, and three days after admission her platelet-count was 60,000 per c.mm. She died three weeks after the start of her illness. Permission for necropsy was not granted.

Discussion

All these cases seem to have been examples of the syndrome of uræmia, hæmolytic anæmia, red-cell fragmentation, and thrombocytopenia which has previously been described by Gasser et al. (1955) and Allison (1957). These workers suggested that the syndrome had a common precipitating cause—although each found that the underlying pathology was different. Thus in all five children described by Gasser et al. (1955) necropsy showed bilateral renal cortical necrosis, which in one was secondary to thrombotic microangiopathy (Symmers 1952); and Allison (1957) found multiple platelet thrombi in both kidneys in his two fatal cases. Despite certain striking similarities in the clinical and hæmatological features, nothing suggests a uniform ætiology in our series: the renal lesion in case 1 was essentially acute glomerulonephritis, in case 2 bilateral cortical necrosis, and in case 3 an acute urinary infection. The pathogenesis of the red-cell defect in case 4 and in case 5 remains unknown, but the raised osmotic fragility in case 4 again suggests that it was different from that in cases 1–3 and in case 5. The clinical and laboratory features in the previously reported series and in our cases are summarised in the accompanying table.

It is now well recognised that anæmia and thrombocytopenia may occur in some patients with uræmia. Many workers have shown that the anæmia of uræmia has a dual origin in bone-marrow depression (Kaye 1958) and in shortened red-cell life (Chaplin and Mollison 1953, Joske et al. 1956, Kaye 1958). Joske et al. (1956) showed that the hæmolytic component usually developed late in the disease, carried a poor prognosis, and was due to some extracellular factor acting on intrinsically normal red cells. Aherne (1957) noted raised reticulocyte-counts and pronounced polychromasia in some of his cases, and we have also occasionally found raised reticulocyte-counts in uræmia—especially in the terminal stages of a chronic illness. In the present series, however, the anæmia was unusually severe and was associated with an increase in reticulocytes and with the appearance of normoblasts in the peripheral blood; despite this, two of the patients recovered.

Red cells with bizarre shapes have been noted both in uræmia and in hæmolytic anæmia. Schwartz and Motto (1949) first described a distinct form of poikilocyte, the " burr " cell, which appears in large numbers in uræmia. They also noted these cells in gastric carcinoma and in bleeding peptic ulcer, while others have seen them in cases of acute hepatic necrosis and after splenectomy (Dacie 1954). The pathogenesis of the cell defect remains unknown—although Aherne (1957) showed that in uræmia burr cells tended to be associated with a steadily rising blood-urea, especially in the terminal phases of an illness, and with a urea level of over 150 mg. per 100 ml. He was unable to produce burr cells by incubating normal or traumatised red cells with urea or with uræmic plasma. Dacie et al. (1953) described a " triangular " cell in hæmolytic anæmia which they thought was entirely different from the burr cell. Dacie (1960) considers that the triangular cell is always associated with increased hæmolysis, and that it is probably a prehæmolytic form. Most of our cases showed both types of red-cell distortion, and in two cases it was the presence of numerous triangular cells which first suggested the diagnosis. It seems likely that the bizarre poikilocytosis which is such a conspicuous feature of this syndrome is a direct but non-specific reflection of the coexistent uræmia and hæmolytic anæmia.

Willoughby (1960) found that significant thrombocytopenia complicated about 15% of cases of uræmia with bleeding; in his own series platelet-counts of below 100,000 per c.mm. were found in four out of twenty-two patients with hæmorrhagic symptoms and in one out of twenty-eight patients without such symptoms. Four of our patients had platelet-counts of less than 100,000 per c.mm. at some stage of their illness; in the fifth the count on admission was 104,000 per c.mm., but the history of bruising and purpura suggests a lower count at an earlier stage.

Thus, though all the features of this syndrome have been described in uræmia, their simultaneous occurrence in adults must be rare—and if found would suggest the diagnosis of thrombotic thrombocytopenic purpura. As Allison (1957) pointed out, this condition differs from the red-cell fragmentation syndrome in children in its frequent association with neurological disturbances and in its invariably fatal outcome. All but two of the seventeen reported cases of the red-cell fragmentation syndrome have been in children under 15 months old; and we suggest that the condition is better regarded as an occasional manifestation of primary renal failure (from whatever cause) in young children than as a disease entity. This is supported by the considerable differences in the clinical and pathological features of the syndrome among these seventeen cases (see table). The difference between the reaction of the adult and the infant to uræmia may possibly be due to the negligible bone-marrow reserve in infancy.

Any child who is found to have bizarre poikilocytes of the type described should be fully investigated hæmatologically and have a blood-urea estimation. The syndrome may be commoner than the reported cases suggest, and increasing recognition may lead to a better assessment of the various forms of treatment and of the prognosis.

Summary

Each of five children had uræmia, hæmolytic anæmia, thrombocytopenia, and fragmentation of the red blood-cells.

Neither the clinical nor the pathological features pointed to a common underlying ætiology, and all the hæmatological changes may have been a manifestation of acute uræmia in young children.

The condition seems to be commoner than the seventeen reported cases would suggest, since these five patients were seen during an eighteen-month period at one hospital.

Any child with a blood-film showing bizarre poikilocytosis, and especially " burr " and " triangular " cells, should have a full hæmatological investigation and a blood-urea estimation.

We wish to thank the physicians and surgeons of the Hospital for Sick Children for permission to publish details of their cases; Dr. Martin Bodian for the necropsy reports; and Dr. P. R. Evans, Dr. R. M. Hardisty, Dr. R. Sephton-Smith, and Dr. M. I. Willoughby for their advice and help.

References overleaf

AVERAGE FLUID VALUES AND ELECTROLYTE NEEDS

An Introduction to a "Guessing Chart"

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THE problem of adequately maintaining body fluids and electrolytes is one which arises with many patients. Adequate balance is best achieved when based on physiological facts. The consideration of basic information, from which most rules-of-thumb are derived, is especially valuable with children, in whom body size and needs vary so greatly.

The chart (see figure) is an attempt to place some essential data on a single pocket-sized card. It was developed in 1957 when I was working in the burns unit at the Birmingham Accident Hospital. Since then it has been used in a wide range of clinical problems other than burns, such as postoperative fluid maintenance, blood-transfusion (especially that associated with operation or accidental trauma), and oliguria and anuria of whatever cause.

The base line of the chart is a height-weight-age scale. Below it are the corresponding blood-volumes, red-cell volumes, venous hæmatocrit values, and hæmoglobin values. On the left side are the daily intake needs of water, calories, and common electrolytes, these being related to the height-weight-age scale by the central graph line. On the right side of the chart are shown the daily water losses, subdivided into three components of urine volume, insensible loss, and fæces water. These amounts are also related to the height-weight-age scale by the central graph line.

Single values may prove misleading, but in clinical practice it is necessary to specify them for the nurses to follow. For this reason single values are given here; it so happens that most of the average values vary by about ±20% of the volume shown.

Expected clinical use has influenced selection of the amounts shown. Some are chosen near upper maintenance limits, some near the lower, and some between these requirements. This has resulted in the fluid intake and output being unequal.

The title "guessing chart" is used to discourage unjustified reliance on these figures. To represent the requirements in health at rest by a single figure compels some inaccuracy, but this is acceptable when precision is not essential. There is no adequate substitute for measuring fluid exchange and calculating replacements after clinical assessment, which should include state of hydration, signs of circulatory failure, and the clinical response to the administration or withholding of therapy.

Amounts have been reckoned per kilogramme of body-weight per day (twenty-four hours), rather than per unit of surface area, because the height-weight scale is required for the most accurate assessment of blood-volume (Davies and Topley 1956), and the use of surface area is open to other objections (Oliver et al. 1958).

This chart shows body-maintenance values only—i.e., the amounts which are found in, or lost and replenished by, a normal person. Disease may result in extra losses which may call for extra replacement, but abnormal losses cannot be shown legibly on this chart, which it must be re-emphasised is related to normal maintenance only.*

Examples of Use of Chart

Blood-transfusion

If it is desired to restore the normal hæmoglobin level in a patient who is anæmic the amount of blood required is readily calculated.

Example.—A 6-year-old child who weighed 21 kg. had a hæmoglobin of 7 g. per 100 ml. According to the chart his blood-volume was about 1500 ml. and his normal hæmoglobin was 13·5 g. per 100 ml. The hæmoglobin level was about half his normal and, therefore, he required about half his blood-volume—i.e., 750 ml. of normal blood. Citrated bank-blood was used, which had been diluted with the customary 120 ml. of sodium citrate per 540 ml. bottle, so the calculated deficiency of normal blood was increased by between a quarter and a fifth to equal the same amount of citrated blood. In this example, the 750 ml. calculated as the deficiency of normal blood was increased to 920 ml. of citrated bank-blood.

When acute blood loss associated with trauma is being corrected, the hæmoglobin dilution is a delayed indicator and the amount of blood transfused is better based on clinical assessment (Fisher 1958), helped by a knowledge of the usual losses associated with the particular injury (Clarke et al. 1955, Clarke and Fisher 1956, Clarke 1959). If large volumes are needed, measurement of the actual blood-volume may be of great assistance, and for this purpose the red blood-cell volumes are indicated on the chart.

Water and Electrolyte Intake

Maintenance amounts are reckoned by multiplying the weight of the patient (in kilogrammes) by the number shown on the chart under "Intake/Day"; this number is related to the weight by the central graph line. The water volume advised for intravenous infusion is three-quarters of the amount shown on the chart as "Intake/Day". The intravenous requirements are best given by deciding first the amount of water and of sodium needed and then calculating the concentration of sodium chloride which would combine these two amounts. The solution should be made isosmotic by the addition of dextrose. Often this can be expressed in amounts of a standard solution such as 0·18% sodium chloride with 4·3% dextrose (sometimes called "one-fifth normal") and using 5% dextrose solution in addition to avoid excess salt. The required amount of potassium can be added to this solution; and potassium can be safely administered in concentrations up to 40 mEq. per litre of intravenous fluid provided that urine flow is adequate.

Example.—A boy of 14 who weighed 50 kg. was being maintained on parenteral fluids only, several days after operation. He had no abnormal fluid loss. The amount of water given each day was three-quarters of 60—i.e., 45 ml. per kg. This volume of 2250 ml. per day was ordered at a rate of 95

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* In the discussion which follows an attempt has been made to quote the original sources of the information. In addition, the more readily available references have been listed separately as "Notes on the Chart". This list is intended to accompany the chart in the pocket.

ml. per hour. The amount of sodium ion required was about 50 times 1·4—i.e., 70 mEq. of sodium. As 0·18% sodium chloride contains 31 mEq. of sodium per litre, 2250 ml. gave just the desired amount. The solution was made isosmotic with 4.3% dextrose.

The amount of potassium needed was also 70 mEq. per day. The intravenous fluid was given in 500 ml. bottles so $4^1/_2$ bottles were given, daily. Potassium chloride 1 g. was added to each bottle, which actually gave him 61 mEq. daily, but this approximation was accepted.

For the first thirty-six hours after operation 5% dextrose solution only was given, and at a rate of half that shown on the chart—i.e., 30 ml. per kg. No electrolyte was given until thirty-six hours after operation.

Treatment of Burns Shock

The blood-concentration which follows the plasma loss of severe burning is most accurately indicated by serial hæmatocrit readings. Since the hæmatocrit value is simply red-cell-volume/blood-volume then any change not caused by red-cell loss or destruction must be the result of alteration in the blood-volume caused by plasma loss.

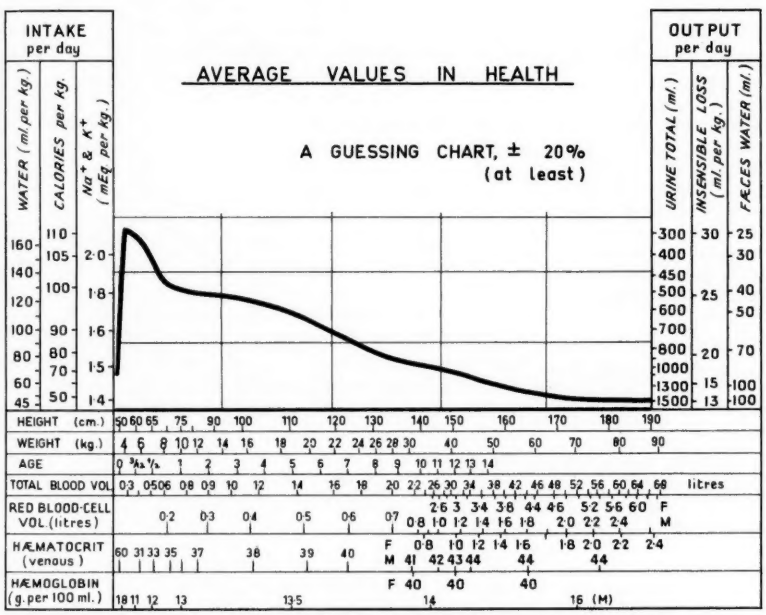
Example.—A 7-year-old girl, weighing 23 kg., had a scald of 20% of her surface area, and her venous hæmatocrit value was 44% (corrected for trapped plasma) two hours after the time of injury. It was reckoned from the chart that this was an increase of one-tenth, as the normal venous hæmatocrit value was assumed to be 40%. Since the red-cell loss is small in a burn of this area, and is slight in the first twelve hours of most burns, including full thickness burns up to 15% of the surface area (Davies and Topley 1956), the change in hæmatocrit value must have been the result of a reduction in blood-volume by one-tenth. Since the blood-volume in this child was about 1700 ml., the reduction was 170 ml. This means that about 170 ml. of burns exudate had been lost in two hours, so the rate of loss was 85 ml. per hour. This was the rate at which the colloid solution was infused intravenously, after the loss of 170 ml. had been rapidly replaced. Repeated hæmatocrit estimations at hourly, and later at longer intervals, provided a check on these calculations.

Red-blood-cell destruction or loss may be measured directly by radioactive technique using ^{51}Cr or ^{32}P, or it may have to be assumed. A rough guide is that in burns of more than 25% of the body area, especially if they are deep, about 20–40% of the blood-volume should be given as stored blood.

If less detailed management of the shock phase is necessary then one of the formula methods may have to be used, though supervision by this technique is liable to considerable inaccuracy. One such approximate formula is to give intravenously an amount of colloid solution equal to one blood-volume for each 20–25% of the body area burned. This amount is the total colloid given usually over twenty-four to thirty-six hours (Jackson 1959). The water intake for this period should be given in addition to this colloid infusion.

Anuria and Oliguria

When the renal output ceases or almost ceases the intake of maintenance electrolyte should be stopped completely and great care taken to provide only as much water as is lost. Even a slight excess of water daily may amount to considerable overhydration after seven to ten days. For this reason the values shown for insensible loss are basal and can be readily calculated from the chart.



1 g. NaCl. = 17 mEq Na^+
1 g. KCl. = 13·5 mEq K^+

1 g. GLUCOSE → 4 Cal. AND 0·55 ml. WATER OF OXIDATION
1 g. PROTEIN → 4 Cal. AND 0·41 ml. WATER OF OXIDATION
1 g. FAT → 9 Cal. AND 1·07 ml. WATER OF OXIDATION

NOTES ON THE "GUESSING CHART"

This chart is at best a very rough guide to average values in health at rest. The water and calorie intakes suggested are liberal, the electrolyte intake and insensible losses shown are near basal. Maintenance needs only are shown.

When parenteral fluid only is given the water intake shown should be reduced by about a quarter. After severe injury or major operation the maintenance water intake for the first 36 or 48 hours may be reduced by about half the amount shown.

The fluid needs in the first week of life are much less than in subsequent weeks.

The venous hæmatocrit values shown are corrected for trapped plasma. The body hæmatocrit is one-tenth less than the venous.

To convert pounds to kilogrammes divide by 2 and reduce that amount by one-tenth—e.g., 10 lb. is 4·5 kg.

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Silver; p. 65.
Medical Vade-mecum; p. 25.

Calorie Intake
Nelson; p. 100, table 17.
Silver; p. 65.

Na and K Intake
Nelson; p. 194.
Medical Vade-mecum; pp. 25, 27.

Urine Output
Nelson; p. 1011.
Macy; p. 118.

Insensible Loss
Macy; p. 114.

Fæces Water
Macy; p. 123.

Water of Oxidation
Macy; p. 114.

Height-Weight-Age Scale
Nelson; p. 50.
Silver; inner cover.
Medical Vade-mecum; pp. 77, 79.

Blood-volumes and Hæmatocrit
Davies and Topley (1956) *Clin. Sci.* **15**, 135.

Hæmoglobin
Nelson; p. 1403.
Medical Vade-mecum; p. 163.
Silver; p. 572.

The fæces water should be included in the reckoning. The water intake must allow for the water of oxidation of any food given, and this can be estimated from the figures recorded underneath the chart. This water balance should be checked by daily weighing when possible.

Data on which Chart is Based

Daily Intake

The scale shows amounts likely to suit most patients at rest in bed, but does not allow for additional losses.

Water.—The required water intake when there is no abnormal loss depends on the urine volume. Other sources of water loss are fixed and potentially measurable for each case, but the urine volume can be manipulated by varying the water intake. The optimal amount of urine depends on the renal-solute load, which in health is determined by the food intake.

In a 70 kg. adult a customary diet will result in a daily renal-solute output of about 1200 mM; when fasting the solute load is reduced to 800 mM daily. If enough glucose is given to produce the physiologically desirable protein sparing, sodium sparing, and antiketogenic actions, then the urine-solute load is least, about 400 mM daily (Gamble 1954).

The healthy kidney can dilute the renal-solute load to 10 ml. of urine per 1 mM of solute (0·1 M per litre) and can concentrate to 0·7 ml. of urine per 1 mM of solute (1·4 M per litre). It is wise not to expect the kidney under stress to concentrate to more than 2·5 ml. of urine per 1 mM of solute (Talbot et al. 1953). The maximum dilution under stress may be reckoned to be about 5 ml. per 1 mM (0·2 M per litre), though no precise information is available on this point.

If excess water is given, water intoxication may follow; and if insufficient water is supplied dehydration and its sequelæ may then occur.

To consider further the case of a 70 kg. adult: if a fluid intake of 45 ml. per kg.—i.e., 3150 ml.—per day is given, and if insensible loss is minimal at about 1 litre, and if the fæces water about equals the water of oxidation of food, then about 2 litres will be the daily volume of urine. If the urine-solute load is 1200 mM then it will be at a concentration of 1·7 ml. of urine per 1 mM of solute (0·6 M per litre).

Clinical problems are often associated with an intake of water and glucose only, when the renal solute load is at the minimum of 400 mM per day. If the daily water intake remains at 45 ml. per kg. and the insensible loss is basal, the urine-solute concentration will be 5 ml. of urine per 1 mM of solute (0·2 M per litre). As has been mentioned, this is at least as much dilution as is to be expected of a healthy kidney under stress.

If clinical circumstances are such that the renal-solute load and the insensible loss are at a minimum, the fluid intake shown on this chart represents maximal amounts. The kidney is probably best able to cope with a solute load of about 3 ml. of urine to 1 mM of solute (0·33 M per litre) (Darrow 1959), which is near the serum-solute concentration of 3·6 ml. of serum to 1 mM of solute.

Therefore under certain circumstances, such as maintenance parenteral-fluid therapy, it is advisable to reduce the maintenance water requirements to three-quarters of that shown on the chart.

In infancy the urine-solute load and dilution is similar to those mentioned, if the water intake is increased by the amounts shown (Darrow and Pratt 1950).

The fluid needs of the first week of life are much reduced:

The usual reckoning is to allow one-seventh of 165 ml. per kg. (24 ml. per kg.) on the first day of life, increasing by the addition of one-seventh (24 ml. per kg.) on each day so that after seven days the full quantity is being given—i.e., 165 ml. per kg. ($2^1/_2$ oz. per lb.).

The effect of activity, climate, diet, and ill health may be considerable. Changes associated with injury are discussed briefly under the heading " Illness of Trauma ".

An apparatus is now available which measures urine or serum osmolarity quickly and accurately. Measured urine osmolarity will probably be used to guide water therapy more than the assumptions which have been discussed.

Calories.—The caloric requirements reflect the falling metabolic rate associated with ageing, though the relatively small decrease of old age is not shown. The figures quoted allow for normal activity, and resting values are about two-thirds of those recorded here. An increase of 8% occurs for each 1°F rise of body temperature above normal.

Electrolytes.—Electrolyte needs have not yet been precisely defined (Holliday and Segar 1957). Because surgical experience suggests that a frequent error is to give excess electrolyte by vein, especially in the young, the amounts shown here are near basal needs but are adequate for maintenance (Talbot et al. 1959). In active healthy children, the sodium and chloride content of a normal diet is about double or slightly more, and the potassium content about double or slightly less than the corresponding figures shown on the chart (Macy 1942). The sodium content of human milk is about 7 mEq. per litre. Thus a 5 kg. baby receiving 165 ml. of breast milk per kg. daily will be receiving only 1·2 mEq. of sodium per kg.

Larger maintenance amounts are advisable when considerable losses are expected and when the extra loss may be difficult to assess, as with infantile diarrhœa or persistent vomiting. These extra losses are, of course, distinct from maintenance needs and should be added to provide a balanced intake.

As no single value is precise, the sodium and potassium intakes are shown as similar amounts, and these same figures also indicate approximate chloride needs.

Daily Output

Urine.—The proportion of water intake which is passed as urine depends on how much water is lost by extrarenal routes. Usually about half the water intake is voided—in infants slightly less, in adults slightly more.

The amount of urine passed is usually of importance when patients are receiving parenteral fluids. The urine volume shown on the chart is that calculated on the basis of water intake which is three-quarters of that shown on the chart—i.e., the amount recommended for intravenous infusion. This calculation is necessary because there is inadequate published information on this point, except for infants and adults.

Insensible loss.—This needs very careful reckoning in patients who are oliguric or anuric. As these patients are commonly lying immobile in bed, and because over-hydration is a danger, the values shown are near basal and do not allow for sweating (Benedict and Root 1926). If there is much activity or fever, the insensible loss, including sweat, may be double or more that recorded here (Levine et al. 1929). Measurements of healthy patients at rest in bed and not sweating shows the average insensible loss in infants and children to be almost double the basal amounts shown on the chart, but after adolescence the loss is very little more (2–4 ml. per kg.) than the basal amount recorded (Heeley and Talbot 1955).

Fæces water.—This is not a significant loss in health and about equals the water of oxidation (Macy 1942).

Body Normals

The relation of total blood-volume, red-cell volume and hæmatocrit value to the height-weight-age scale is as given by Davies and Topley (1956), save that the height scale is slightly altered for the period from 0 to 3 years. Most emphasis should be given to the height and the body-weight in lean persons, and the age should be a secondary consideration.

The body hæmatocrit value is a tenth less than the venous hæmatocrit, after the latter has been corrected for trapped plasma.

That all these values commonly vary $\pm 10\%$ is not emphasised sufficiently by the chart.

The Illness of Trauma

The changes which follow severe injury or illness cannot be represented on a chart such as this, because these vary with the degree of illness or trauma.

A severe injury, such as a compound fracture of the tibia or femur, or an operation, such as colectomy or partial gastrectomy, is followed by changes that have been well measured and described by Moore and Ball (1952), and that have been reviewed by Cuthbertson (1960). Sodium output was sharply reduced, and to avoid excess sodium administration Moore and Ball (1952) advise withholding sodium for several days after operation. Potassium loss was slightly reduced; but, after a period of several days without intake, a significant deficit had accumulated, and therefore potassium should not be withheld after the third day.

The alterations in water requirements are more difficult to assess (Dudley et al. 1954). The antidiuretic effect of trauma may result in adults in a diminution of urine volume by half, for up to two days after operation. The water maintenance after a major operation may thus be reduced, and may be reckoned as about half the liberal amounts shown on the chart.

More recent investigations, however, suggest that many of the changes which have been regarded as inevitable after trauma may, in fact, be simply the effect of inadequate blood replacement (Flear and Clarke 1955, Topley and Fisher 1956). The response to injury in the neonatal period is different from that in the adult (Rickham 1957, Colle and Paulsen 1959, Young et al. 1959, McCance 1959).

Summary

A chart is presented which shows on the baseline a height-weight-age scale and the related total blood-volumes, red-cell volumes, and hæmoglobin values.

This height-weight-age scale is also related to a suggested daily intake quota on the left and daily water output volumes on the right of the chart.

The water and calorie intakes suggested are high; the electrolyte intake and the insensible loss figures are low. The urine volumes are those expected in most patients at rest in bed, receiving the amount of water advised for parenteral fluid therapy which is three-quarters of the amount shown on the chart as water intake.

Examples show how the chart can be used with blood-transfusion, with maintenance water given intravenously and electrolytes, and in the management of burns shock.

This chart was compiled at the Birmingham Accident Hospital. The stimulus and help offered by all members of the burns unit is gratefully acknowledged, and thanks are especially due to Dr. J. P. Bull, clinical director of the Medical Research Council's Industrial Injuries and Burns Research Unit, for advice during the preparation of this paper. Thanks are also due to the many colleagues who have used the chart in varied clinical problems and made comments which have become the basis of this paper.

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THE RELATION BETWEEN CALORIE INTAKE AND BODY-WEIGHT IN MAN

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ORTHODOX teaching is that a heavy man or woman needs more food than a light one. The Second Committee on Calorie Requirements of F.A.O. (1957) gives three formulæ which relate energy expenditure to body-weight, and which are recommended for use in calculating the dietary needs of large groups. According to these formulæ men weighing 75 kg. require about 550 kcal. a day more than men weighing 60 kg., assuming a similar degree of physical activity. The formulæ are based on many measurements by indirect calorimetry showing that energy expenditure under basal conditions, during walking and many other physical activities, increases with increasing weight.

In healthy populations, it seems reasonable to infer that the heavier members will eat considerably more food than the light. Our purpose here is to show that observed facts, surprisingly, do not accord with this.

Sources of Information

Data on calorie intake and body-weight have been collected from the following surveys *:

1. On 489 primigravidæ of all social classes in Aberdeen, between 1950 and 1953 (Thomson 1958). Thomson and

* The survey methods are fully described in the original papers.

Billewicz (1961) have described the Aberdeen dietary data in relation to the height, weight, and weight-for-height of their subjects; more detailed discussion will be found in their paper.

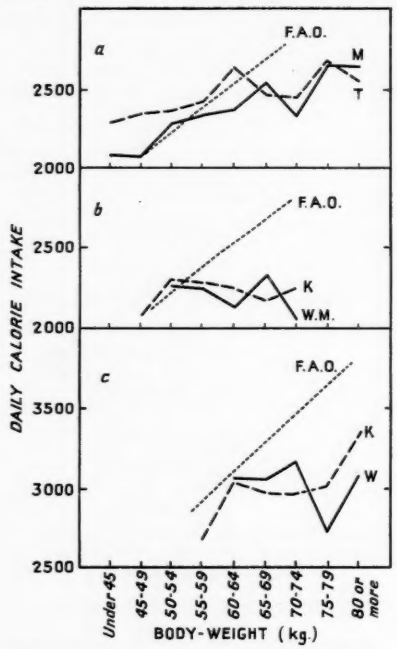
2. On 130 pregnant women, of varying parity and social class, in Britain before the second world war (McCance et al. 1938).

3. On 63 men and 63 women, mostly middle-class, living in or near London before the second world war (Widdowson and McCance 1936, Widdowson 1936).

4. On 113 male and 162 female students at Edinburgh University in 1948 (Kitchen, Passmore, Pyke, and Warnock 1949).

Results

The figure shows the average daily calorie intakes of (*a*) pregnant women, (*b*) non-pregnant women, and (*c*) men, grouped according to body-weight. In each figure the F.A.O. requirement standard is also plotted as a dotted line. In group (*a*) no extra allowance for pregnancy was made: pregnancy would be expected to raise the requirement, but there is no reason to think that it would alter the slope of the line. In each group there are two sets of quite independent data which, despite fluctuations due to small numbers, show good agreement. In no group does calorie intake increase with weight in accordance with the trend of the requirement standard.



Average calorie intakes, according to body-weight, in (*a*) pregnant women, (*b*) non-pregnant women, and (*c*) men. The dotted line shows the calorie requirement predicted from the formulæ of F.A.O. (1957).

Sources: T = Thomson and Billewicz (1961), M = McCance et al. (1938), K = Kitchen et al. (1949), WM = Widdowson and McCance (1936), and W = Widdowson (1936).

Discussion

Other workers also, in America and South Africa, have not found much relationship between food intake and body-weight in female students (Davis and Scoular 1957), in male and female students (Walker 1959), and in soldiers (Grossman and Sloane, 1955). Thus the evidence points clearly to the conclusion that, within the "normal" range of weights at least, increasing weight is not accompanied by much rise in food intake. Since the physiological evidence that extra weight involves extra energy expenditure at rest and during exercise is incontestable (Kleiber 1947, Passmore and Durnin 1955), it follows that heaviness is generally associated with diminished physical activity.

The data presented in the figure were all obtained from apparently healthy subjects. Several studies (Swanson et al. 1955, Johnson et al. 1956, Stefanik et al. 1959) indicate that obese subjects do not as a rule eat more than non-obese controls and may indeed eat less. In obesity, sloth may be more important than gluttony.

The reason why increasing weight appears to be associated with diminishing physical activity rather than with increased appetite is a problem for physiological study. In public health, the question of what allowance, if any, should be made for the body-weight of the subjects in assessing calorie needs seems to require reappraisal.

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21—TRISOMY/NORMAL MOSAICISM in an Intelligent Child with some Mongoloid Characters

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THE term mosaicism, in cytogenic usage, describes a condition in which a substantial minority of cells differ from the majority in their chromosomal content. In man, the condition was first described in Klinefelter's syndrome (Ford et al. 1959), and it has been reported in relation to several other conditions involving the sex chromosomes (Fraccaro et al. 1960, Hirschhorn et al. 1960, Jacobs et al. 1960).

Mosaicism can be regarded as existing in vivo if the possibility of cultural change can be excluded by consistent chromosome analysis of the two cell types in one short-term culture or two long-term cultures. The situation reported here seems to be an example of mosaicism involving cells with a normal female chromosome complement, and cells with an extra small acrocentric chromosome in a patient with certain clinical features of mongolism.

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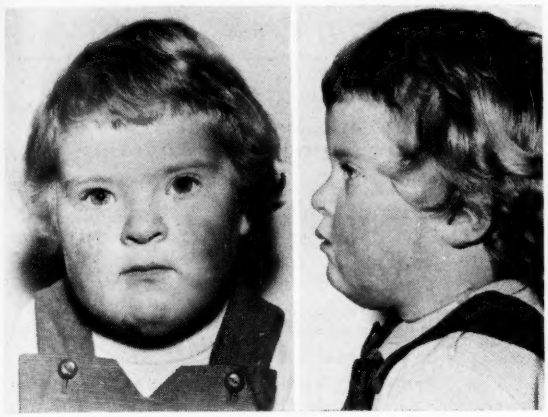

Fig. 1—Appearance of the child at 2 years 3 months.

Case-history

The child was firstborn (Aug. 17, 1958) of healthy parents, both aged 26, and unrelated, after a normal full-term pregnancy. Birth-weight 7 lb. The experienced general practitioner, after considering the possibility of mongolism at birth, thought the baby was developing normally during an uneventful neonatal period and infancy. She sat up at $7^1/_2$ months, and was referred to one of us (V. S.) at 11 months after the question of mongolism had been raised again at the infant-welfare clinic.

Examinations

At *11 months.*—A well-grown child, with good muscle tone, and weighing 20 lb., she had fair curly hair. Her expression was friendly and intelligent, although definitely mongoloid, with slanting eyes. The shape of head and pinnæ was within normal limits, and no third fontanelle was detected. There were no horizontal palmar creases on the hands, and the little fingers were rather short. No congenital heart lesion was detected. She could move across the floor on her seat, stand for 2 minutes with support, and say "Mum" and "Dad", and she knew the dog by name. The overall picture was thought to be against a diagnosis of mongolism, but the child was referred for cytogenetic investigation because of unusual features.

At *16 months.*—Weight $24^1/_2$ lb. Progress seemed normal.

At *17 months.*—Palmprints were examined by Prof. L. S. Penrose. Despite the normal *c* line exit between the 4th and 5th digits, and the low quantitative ridge-count of 46, the general findings were consistent with a diagnosis of mongolism. The palmar *atd* angles were 69° (left) and 87° (right). A radial loop was present on the 4th digit, and the thenar patterns were absent.

At *18 months.*—A skin-biopsy specimen was referred to Dr. C. E. Ford's group at Harwell (see cytological findings).

At *22 months.*—Peripheral blood and skin specimens were taken for culture (see cytological findings). The child was seen by the consultant clinical psychologist, Miss M. A. Davidson, who reported (June 11, 1960): "This little girl was not able to cooperate on formal tests at the 2-year-old level, but the Vineland social maturity scale was completed with the parents. On this her social competence seems reasonable for a child of her age."

At *2 years.*—She was healthy, played normally with other children, and recognised and named pictures of animals.

At *2 years 3 months.*—Re-examination (V. S.) showed retention of mongoloid features, but both mental and physical progress had been good (fig. 1); height 33 in., weight $30^1/_4$ lb. The anterioposterior skull measurement was $6^3/_4$ in., and the lateral diameter was $5^1/_4$ in. Her behaviour in the consulting-room was entirely normal.

A further report was received from Miss Davidson: "On Dec. 5: revised Stanford-Binet form 'L' C.A.2.3, M.A.2.3, I.Q.100. The child has developed very well since I saw her last in June . . . is now able to cooperate fully on the revised Stanford-Binet, and the test results suggest that she is at least of average ability. It is clear that she is far too young for any I.Q. assessment to be valid, and she may well turn out to be a good deal better than the above result suggests."

CHROMOSOME-COUNTS IN PERIPHERAL BLOOD AND SKIN CULTURES

Tissue	Chromosome-counts				% cells with 47 chromosomes
	46		47		
	Counted	Analysed	Counted	Analysed	
Skin—1st culture	38	23	18	10	47
Skin—2nd culture	16	13	10	5	62
Peripheral blood ..	11	11	0	0	0
Totals ..	65	47	28	15	43

A peripheral blood-film was examined by Dr. F. G. Bolton (Dec. 16): "The peripheral blood-film seems entirely normal. Drumsticks are present in normal numbers. There is no failure of segmentation of polymorphs, and there seems no evidence for the existence of two classes of leucocyte."

Cytological Observations

The skin specimens were cultured by the method described by Harnden (1960). For the peripheral blood leucocytes, a slightly modified version of the technique of Hungerford et al. (1959) was used. The chromosome-counts are summarised in the table.

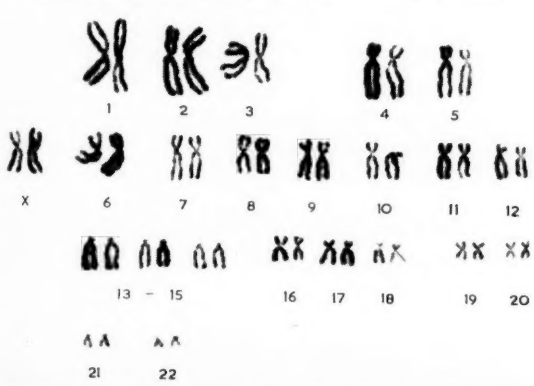

Fig. 2—Chromosome array from cell with 46 chromosomes (Denver system).

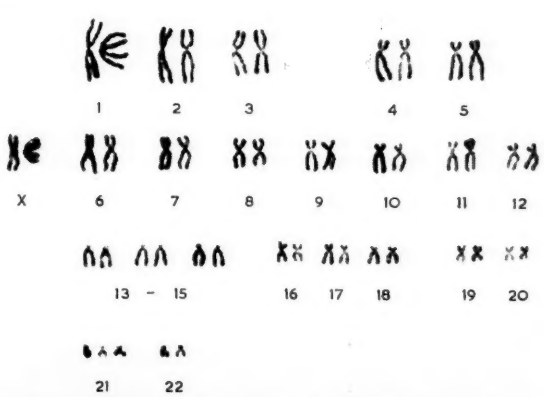

Fig. 3—Chromosome array from cell with 47 chromosomes.

Cells of two types were found in cultures set up from skin specimens from different parts of the body, taken at 18 and 22 months. All analysed cells with 46 chromosomes contained a normal female karyotype, as in fig. 2. The analysed cells with 47 chromosomes were trisomic for chromosome 21, as in fig. 3. In the culture of leucocytes from peripheral blood, only 11 dividing cells of a suitable standard were examined, all of which carried a normal female chromosome complement.

Discussion

This case is clinically confusing, having many of the individual stigmata of mongolism, but no evident physical or intellectual retardation. Cytological examination shows the presence of both normal and " mongol " cells in cultures from two very small specimens of skin. This suggests that the two cell types are thoroughly intermixed in the dermis. Of course, the proportion of cells with 46 and 47 chromosomes in long-term cultures does not necessarily represent the in-vivo proportions of the two cell types in the dermis. So far as the lymphocyte series is concerned, it is probably safe to infer that the majority of cells have 46 chromosomes, since 11 successive cells were normal. Selective proliferation of the normal cells in tissues with a high mitotic index, as in bone-marrow, might lead in time to a higher overall percentage of normal cells in the body. These investigations give no guide to the more important question of the proportion of abnormal cells in the brain. The child has well-marked Brushfield spots, and, considering the neuroectodermal origin of the iris where these lesions arise, this suggests involvement of the nervous system.

The mosaicism reported here may have originated in two ways. A normal cell with 46 chromosomes may have arisen in a trisomic embryo as a result of mitotic non-disjunction or the exclusion of a small acrocentric chromosome from the telophase nuclei after anaphase lagging; alternatively, there may have been non-disjunction involving chromosome 21 in a normal diploid embryo some time after the first cleavage division. This would result in a presumably inviable cell with 45 chromosomes, and a cell with 47 chromosomes from which the " mongol " cell population could have arisen. Whether one presupposes a normal or trisomic zygote, the chromosome results and clinical findings (such as mongol palmprints, Brushfield spots, and average intelligence) can only be reconciled with mosaicism arising at an early developmental stage.

Clearly, cases of suspected mongolism which are clinically confusing cannot necessarily be resolved without studying many cells and, wherever possible, more than one tissue. Since it seems possible that mosaic mongols may sometimes be phenotypically normal but produce a high proportion of affected gametes, the possibility of mosaicism deserves consideration in the cytological examination of the parents of mongols, or in other conditions in which an extra small acrocentric is present.

We are indebted to Mr. George Clarke and Miss Christine Scammell for expert technical assistance.

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Preliminary Communications

EXPERIMENTAL THYMIC LESIONS RESEMBLING THOSE OF MYASTHENIA GRAVIS

BETWEEN 60 and 70% of cases of myasthenia gravis [1] show characteristic thymic lesions consisting of hyperplasia of the gland with the formation of germinal centres in the medulla. These structures are histologically identical with those seen in lymph-nodes after antigenic stimulation, which are now known to be capable of antibody formation.[2 3] In some cases, slight plasma-cell infiltration is also present in the thymus.

These lesions suggest an immune response in the thymus gland in myasthenia gravis, but interpretation is difficult owing to previous failures to demonstrate histological changes in the thymus glands of immunised animals or to obtain evidence of antibody formation in the organ.[4–7]

METHODS AND RESULTS

To study the reaction of the thymus under maximum antigenic stimulation one lobe of the exposed guineapig gland was directly injected at multiple sites with either a typhoid-paratyphoid vaccine (T.A.B.) or with aluminium-phosphate-precipitated diphtheria toxoid (P.T.A.P.).

Two injections were made at an interval of 2–3 weeks, the guineapigs being killed 5–9 days after the last injection. A dose of 4×10^7 bacilli, or 20 or 1·2 Lf of diphtheria toxoid, in 0·2 ml. saline was employed for each series of injections, the uninjected thymic lobe being used as a control.

In thymic glands directly injected with T.A.B. vaccine germinal centres (fig. 1), histologically identical with those seen in other lymphoid organs, were found in injection areas in the medulla, and in addition some areas showed much plasma-cell formation. Guineapigs injected with diphtheria P.T.A.P. had groups of macrophages filled with alum particles in the medulla; at the periphery of these were wide zones of antibody-containing plasma-cells which were shown by the " sandwich

1. Castleman, B. *in* Atlas of Tumor Pathology. Washington, 1955.
2. Ortega, L. G., Mellors, R. C. *J. exp. Med.* 1957, **106,** 627.
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4. Bjørneboe, M., Gormsen, H., Lundqvist, F. R. *J. Immunol.* 1947, **55,** 121.
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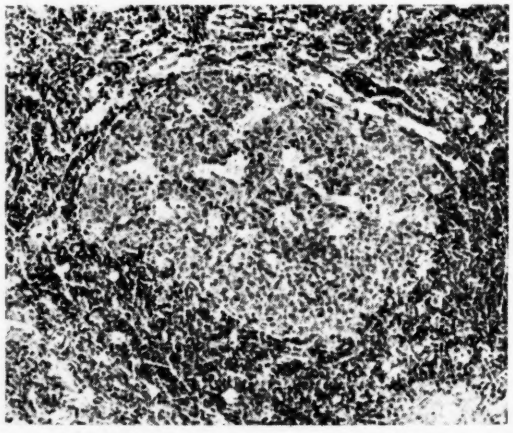

Fig. 1—Germinal centre in medulla of guineapig thymus after direct injection of T.A.B. vaccine. (×170.)

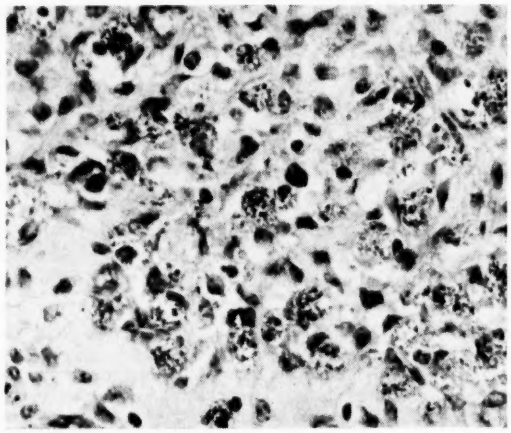

Fig. 2—Storage of trypan blue in medulla of thymus in region of cautery incision. (×410.)

technique [8] to localise a fluorescein-conjugate of diphtheria antitoxin after preliminary treatment of the section with a dilute solution of diphtheria toxoid.

After direct injection of antigens into the thymus, therefore, the histological changes were those usually associated with antibody formation in other lymphoid organs—in contrast to the complete lack of reaction observed by others after introduction of antigens into the blood-stream. This failure of reaction to circulating antigen suggests the existence of a barrier against the entry of antigens into the thymus, and this possibility was investigated by observing the localisation of vital dye or intravenously injected antigen (*Streptococcus pneumoniæ* type III polysaccharide) in the normal and injured gland.

Vital staining of the normal thymus was studied in guinea-pigs and rats after subcutaneous injection of trypan blue in a dose of 2 ml. of 2% solution in rats, and 8 ml. of 1·5% solution in guineapigs. Some animals were given a second injection after 2 days. *Str. pneumoniae* type III capsular polysaccharide was injected by the external jugular or femoral veins in a dose of 10 or 12 mg. in the rat and guineapig respectively. Thymic injury was inflicted by a cautery incision across the lower pole of one lobe of the guineapig gland, vital dye or pneumococcal polysaccharide being injected 30 or 10 minutes respectively after the injury.

Vital staining of the normal thymus was obvious in the histiocytes of the connective tissue of the thymic capsule and interlobular septæ. The medulla of the thymus showed negligible storage of vital dye; in some animals occasional granules of dye were seen in cells usually situated at the corticomedullary junction or the peripheral zone of the thymic cortex. This feeble uptake of dye was not due to absence of reticuloendothelial cells from the normal gland, because staining by metallic-impregnation methods for microglia showed numbers of such cells scattered diffusely in the thymic medulla. The lack of uptake of vital dye in the normal thymus was duplicated by the failure of the gland to segregate intravenously injected pneumococcal polysaccharide. Only slight specific fluorescence was observed in cells in the thymic cortex or medulla when stained by a single-layer technique for pneumococcal polysaccharide, and this was mainly in the region of small blood-vessels—a result similar to that obtained by other observers employing protein antigens.

In the thymus gland of guineapigs injured by a local cautery incision, however, much vital staining of macrophages was found in the medulla (fig. 2); and similarly in animals injected with pneumococcal polysaccharide after thymic injury numerous cells containing polysaccharide were observed in the region of the injury.

8. Coons, A. H., Leduc, E. H., Connolly, J. H. *J. exp. Med.* 1955, **105**, 49.

DISCUSSION

The histological reactions of antibody formation in the thymus after direct antigen injection, and the penetration into the gland and phagocytosis of both vital dye and antigens after local thymic injury, suggest that the normal thymus fails to respond to circulating antigens because of a barrier between the thymus and the blood-stream which may be broken down by local trauma, presumably by an increase in local vascular permeability. The existence of such a barrier in the normal gland would preclude any cellular reaction of the normal thymus to circulating antigen, and any antibody formation in the organ.

These observations provide a basis for a possible interpretation of the lesion in the human thymus in myasthenia gravis. The formation of germinal centres and antibody-containing plasma-cells in the thymus after direct antigen injection suggests that the thymic changes in myasthenia gravis may represent an immune response to an antigen. If the human thymus possesses a barrier to circulating antigen similar to that in animals, such an immune response must arise primarily in the gland itself and not, as suggested by some workers,[9] as a result of a common disturbance producing both the myasthenia and the changes in the gland—a conclusion also supported by the absence of reaction in other lymphoid organs in myasthenia gravis. This would indicate an auto-immune factor in the pathogenesis of myasthenia gravis, either from the sharing of a common antigen between the thymus and motor nerve-endings or because of the formation of a "forbidden clone" of immunologically competent cells, as postulated by Burnet [10] in the development of auto-immune disease. Shielding of the thymus from antigens would seem to facilitate such clonal development, because Burnet postulated antigenic contact as a mechanism for the destruction of such clones as may react against an individual's own tissues.

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TRANSPLANTATION-SENSITISING FACTOR IN DOG URINE

THE basement membranes of the glomerular tuft are one of the first areas to be damaged when a kidney is homotransplanted to a sensitised animal.[11 12] For this reason, we have inclined to the view that kidney antigen, in whole or part, was mucopolysaccharide. Since urine contains a number of mucopolysaccharides about which little is known from an immunological point of view, we decided to test dog urine for its ability to sensitise (in a transplantation sense) normal animals which had been infused intravenously several times. The criterion of transplantation sensitisation was to be rapid rejection of a kidney transplanted from the donor of the urine to the recipients of the urine. If rejection, as manifested by a sudden onset of anuria after a period of secretion, occurred

9. Havard, C. W. H., Bodley Scott, R. *Brit. J. Hæmat.* 1960, **6**, 178.
10. Burnet, F. M. The Clonal Selection Theory of Acquired Immunity. Cambridge, 1959.
11. Dempster, W. J. *Brit. J. Surg.* 1953, **40**, 447.
12. Dempster, W. J. *Brit. J. plast. Surg.* 1953, **5**, 228.

within 40 hours of transplantation this would indicate sensitisation of the recipient.

MATERIALS AND METHODS

All the dogs used in these experiments were female greyhounds, averaging about 22 kg. The general plan was to infuse intravenously three times at weekly intervals a quantity of fresh urine removed from the bladder of a female greyhound. One donor supplied urine to two recipients. The urine was collected from the bladder on the morning the infusion was due to be given. The volume usually collected was about 120 ml. Immediately after collection the urine was spun at 2500 r.p.m. (1400*g*) for 10 minutes, and the supernatant was decanted and infused. The sediment usually contained a few cells. A week after the last infusion of urine the kidneys of the donor were transplanted to the recipients of the urine. The transplantation technique used was that previously described.[11 12]

Assessment of Anuria or Oliguria

As soon as the new circulation had been established in the homotransplanted kidneys they started to secrete dilute urine. This continued for some hours and then stopped. At this stage it was important to demonstrate a true anuria. The dogs all had free access to water after recovery from anæsthesia. They were then given an intravenous infusion of 500 ml. normal saline followed by 300 ml. of 2% saline. A functioning kidney will respond immediately to such an osmotic load; anuric homotransplanted kidneys will not. If anuria proved to be genuine, the transplanted kidney was exposed, the renal vein was cut, and the blood-flow was measured for 15 seconds. The renal artery was clamped, and the kidney was removed and weighed. A section of the kidney was then taken and fixed in formol-saline for histological examination. The whole kidney was examined for any obvious signs—such as infarction or thrombosis—which might explain the anuria on grounds other than immunological.

RESULTS

All the dogs showed an allergic response to the infusion of urine irrespective of whether they later became sensitised in a transplantation sense. Two distinct types of allergic response were observed:

1. *Immediate reaction.*—Within a few minutes of starting the infusion, these dogs began to salivate excessively, became restless, breathed more rapidly, and vomited. This reaction was easily controlled by intravenous injections of adrenaline (2 ml. of 1/1000). In some cases phenergan 2 ml. (50 mg.) given intramuscularly 30 minutes before the infusion seemed to reduce the severity of the reaction.

2. *Delayed reaction.*—The dogs which had a delayed reaction may or may not have had an immediate reaction. Up to 24 hours after the urine infusion six dogs had a delayed reaction. The prodromal symptoms were not observed, and each of these dogs was found expiring. None of them responded to treatment, and all died.

Urine infusion experiments were conducted under the following conditions:

Group 1.—Twelve kidneys were transplanted from six donors. Urine was collected in the morning from the bladder of the donor, spun at 2500 r.p.m. (1400*g*) for 10 minutes, and decanted. The decanted urine was then infused intravenously into the recipients. The immediate allergic reaction was treated with injections of adrenaline. The amount of urine infused was limited by the volume obtained by catheter. The volume infused in each dog (except those noted below) on the three occasions was about 120 ml., and the infusions were given weekly. A week after the last infusion, the kidneys of the urine donor were transplanted to the urine recipients. Urine started to flow within 10 minutes of establishing the new circulation to the homotransplanted kidneys, but the flow stopped at variable intervals afterwards. The relevant data are included in the table.

DATA RELATING TO HOMOTRANSPLANTED KIDNEYS REMOVED AS SOON AS ANURIA WAS ESTABLISHED

Dog no.	Weight of kidney when removed (g.) *	Blood-flow (ml. per min.)	Functional period (hr.)
1	105	120	10
2	105	200	9
3	120	300	20
4	150	180	12
5	130	200	20
6	145	120	10
7	180	60	36
8	140	130	36

* The mean weight of adult greyhound kidneys is 75 g.[13]

None of the above eight anuric kidneys showed signs to indicate a technical cause of anuria. Two kidneys in this group were removed on the 4th day, while still secreting. These dogs were deemed not sensitised. The urine donor in this case was difficult in that only small volumes (about 50 ml. each time) were available from its bladder. Failure to sensitise the recipients may have been due to the small volumes of infused urine. One dog died from excess anæsthesia before anuria arose, and the other died in convulsions after recovering from the anæsthetic. These convulsions resembled those seen in the delayed allergic response.

Group 2.—Four kidneys from two donors were transplanted. Urine was collected as indicated in group 1; but instead of infusing the supernatant, the sediment was made up to 50 ml. with saline, and infused intravenously three times at weekly intervals. A week after the last infusion, the kidneys from the urine donor were transplanted to the recipients. All these transplanted kidneys were removed on the 4th day, while still secreting. These dogs were deemed not sensitised.

Group 3.—Four kidneys were transplanted from two donors. The infusions of urine were given as indicated in group 1. A week after the last infusion, the kidneys from a dog other than the donor of urine were transplanted to the urine recipients. All these transplanted kidneys were removed on the 4th day, while still secreting. These results show that the urine sensitisation was individually specific.

Group 4.—Four kidneys from two urine donors were transplanted. Urine was collected on various days as in group 1. The specimens were then stored at −20°C. Some days later, when the next infusion was due, the urine specimens were thawed out in warm water and then infused intravenously into the recipients. A week after the last infusion, the kidneys from the urine donors were transplanted to the urine recipients. All these transplanted kidneys were removed on the 4th day, while still secreting. The recipient animals were deemed not sensitised.

The fact that freezing destroyed the sensitising factor was disappointing. We had hoped to catheterise dogs and collect urine whenever available because of the occasional difficulty of obtaining urine on the exact day a urine infusion was due.

Group 5.—Six kidneys were transplanted from three urine donors. Because some donors persistently voided their urine before they could be catheterised in the morning, we induced a water diuresis in order to collect large quantities of urine. The urine was spun at 2500 r.p.m. (1400*g*) for 10 minutes, and in this group 250 ml. of dilute urine was infused on each occasion. A week after the last infusion kidneys were transplanted from the urine donors to the recipients. All transplanted kidneys were removed on the 4th day, while still secreting. These recipients were deemed not sensitised.

Histology of the Rejected Kidneys

Rupture of tuft capillaries with protein in the subcapsular space was seen in some kidneys. The overall picture showed

13. Dempster, W. J. *Brit. J. Urol.* 1955, **27**, 66.

remarkably little damage, which was not at all what we had expected in view of previous experience with sensitised dogs.[11 12] Surprised by the lack of damage in the first two anuric kidneys, we took all possible precautions with the others to make certain that they were truly anuric.

DISCUSSION

Since our experiments indicate that some transplantation-sensitising factor is present in urine, and various workers have failed to find any sign of it in plasma, it must be contributed either by the kidney or by the mucosal surface of the lower urinary tract. It may arise in the mucosal cells of the bladder; experiments are in progress to establish this point.

In view of the lability of the urine-sensitising factor—for example, its destruction by freezing to −20°C—it is unlikely to be mucopolysaccharide since such complexes are usually stable when subjected to freezing and thawing. Experiments are in hand to try to isolate and characterise the sensitising factor.

Although the arrest of renal function came within the expected period after transplantation, the histological appearances of the anuric kidneys in group 1 indicate surprisingly mild parenchymal damage. We have no satisfactory explanation of this unexpected result. One should remember that kidneys in non-sensitised animals can also be rendered oliguric with surprisingly little glomerulotubular damage. Possibly only mild sensitisation is evoked by urine infusions.

The expenses involved in these experiments were defrayed by a grant to W. J. D. from the Medical Research Council.

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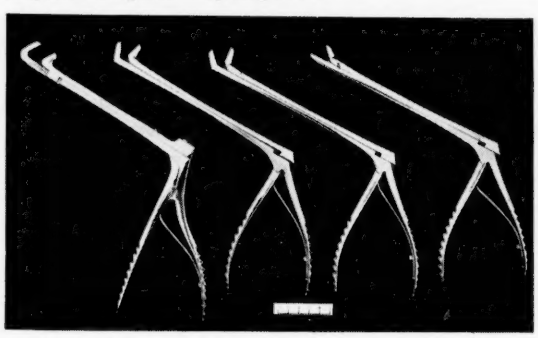
New Inventions

LONG-NECKED DISC AND BONE RONGEURS

ANTERIOR spinal surgery, whether for tuberculosis of the spine, removing neoplasms, or removing discs, requires bone rongeurs with particularly long necks.



The forceps (see figure), specially made for me by Allen & Hanburys, Ltd., Bethnal Green, London, E.2, have been under trial now for three years and have proved successful.

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Reviews of Books

Intra-abdominal Crises

KENNETH D. KEELE, M.D., F.R.C.P., consultant physician; NORMAN M. MATHESON, F.R.C.S., M.R.C.P., F.A.C.S., consultant surgeon, Ashford Hospital, Middlesex. London: Butterworths. 1961. Pp. 397. 50*s*.

Surgery of the Acute Abdomen

JOHN A. SHEPHERD, V.R.D., M.D., CH.M., F.R.C.S., Q.H.S., consultant general surgeon, Liverpool Region. Edinburgh: E. & S. Livingstone. 1960. Pp. 1228. 100*s*.

ABDOMINAL emergencies are the concern of general practitioner, physician, and surgeon, and it is in approach to the subject that the interest of each must vary. The general practitioner needs to recognise the dangers lurking in a symptom or group of symptoms, so that, without necessarily making the exact diagnosis every time, he can at least heed the alarm when it sounds. It is sometimes said, and not without truth, that the most dangerous occasion for someone to have an abdominal emergency is when he is already a patient in hospital. This is because hospital staffs have usually been alerted to the possibility by the time an abdominal emergency reaches hospital; only the symptoms of postoperative emergencies have to be recognised by them as an alert, and the very fact of previous surgery itself calls complications to mind. In comparison with the general practitioner, the surgeon and physician are therefore trained by experience less to notice the red light than to confirm it. A further problem for the surgeon, since he may have to explore, is to make a diagnosis precise pathologically, functionally, and anatomically—a goal not always possible to reach in full.

The two attitudes are well reflected in these books. *Intra-abdominal Crises* is written by physician and surgeon hand-in-hand, with an eye to the practitioner's problems; it seeks to resolve the schism of mind inculcated by years of orthodox teaching (and even by the topography of many casualty departments)—that there are on the one hand "medical" emergencies, on the other "surgical". In the outcome, their work is an essay developing the topic from the initial moment of crisis, gradually unfolding the development and management of the case from that moment. So chapter 1 starts with the background of patient, of the first observer, then general practitioner, to the administrative mechanism of hospital admission in this country—emergency bed service, ambulance and casualty service. Thence to a discourse on presenting symptoms and predominant signs, followed by an intelligent review in chapter 5 of those conditions which may delude by simulating the intra-abdominal crisis. This is the first and most valuable part of the book.

From the general in part 1 to the particular in part 2; and in this lies the closer affinity to *Surgery of the Acute Abdomen*, a considerable work written by one surgeon alone. This has the orthodox approach of the surgically trained; for, after two opening chapters on principles of diagnosis and management, each subject is taken in anatomical order from the top downwards and within outwards. A final chapter on "medical conditions simulating the acute surgical abdomen" reveals the old schism. The merits of this work lie in its completeness, rarities being intentionally included; in an appendix on the incidence of the various disorders leading to emergency operation; and in a full and well-classified bibliography. It is too long to be read as a whole and must be regarded as a work of reference for surgeons in training and already trained. *Intra-abdominal Crises* may be read straight through by student, practitioner, and postgraduate, for though it contains no references it is a concise exposition.

Blood Diseases of Infancy and Childhood

CARL H. SMITH, M.D., professor of clinical pediatrics, Cornell University Medical College, New York. St. Louis: C. V. Mosby. London: Henry Kimpton. 1960. Pp. 551. 127*s*. 6*d*.

NO-ONE is better qualified to write on this subject than Professor Smith. The writer must not only know about diseases of the blood, but also be able to fit this knowledge into

the changing background of normal development. This aspect of children's blood diseases is always prominent in this book, in which conditions peculiar to childhood and those also seen in adults are comprehensively presented. Though the initial chapters on general considerations are rather misleadingly brief, much more information is provided later in the sections on the different diseases; for example, tables showing how the various blood parameters vary with age are found in the chapters on anæmia and so on, rather than in the chapter on blood changes during growth. A very useful chapter on general aspects of anæmia precedes the discussion of the individual anæmias, since "the anæmias constitute the major segment of the blood disorders of infancy and childhood". Professor Smith accepts the existence of juvenile pernicious anæmia but admits that it is very rare and that other megaloblastic anæmias must be excluded. The megaloblastic anæmia associated with malabsorption syndromes receives surprisingly little attention. The book deals very fully with the treatment of leukæmias, and naturally concentrates on the acute leukæmias since the chronic ones are rare in childhood. Professor Smith is unimpressed by the results so far of bone-marrow transplantation. The blood-clotting disorders are given very up-to-date treatment, and it is interesting to see the large amounts of plasma and blood that are recommended for the control of hæmophilic bleeding. The chapters on erythroblastosis fœtalis, the hæmoglobinopathies, and the proper use of blood-transfusion in pædiatric practice are very good; and tables help to clarify the very practical information recorded.

No coloured reproductions of blood or bone-marrow cells are attempted, which is a wise decision since these plates are best collected into special atlases and a few plates in a general book are seldom very valuable and add considerably to the cost. The book should certainly be studied by every hæmatologist and pædiatrician who is anxious to be well informed about this rapidly enlarging subject.

Biological Clocks

Cold Spring Harbor Symposia on Quantitative Biology, Vol. XXV. New York: Long Island Biological Association Inc. 1960. Pp. 524. $8.

THIS admirably produced book contains 50 papers presented last June at the Biological Laboratory, Long Island. After an opening address by Prof. Erwin Bünning, there are eight sections, the first six on various aspects of circadian rhythms. "Circadian" means "once in roughly 24 hours—about a day". The rhythms are found in many forms of animal and plant life; and studies cover geophysical, metabolic, temperature, light, and endocrine influences. Models for circadian rhythms are illustrated in seven papers. Eleven papers on chronometry in celestial navigation discuss the remarkable powers of birds, insects, fish (even the littoral amphipods, sand-hoppers) to choose a particular directional line in space (astronomical orientation). Since navigation implies geometric and chronometric "instruments" to signify space and time dimensions, these very varied creatures may be held to possess such instruments in their structure. Of special note is the finding that the time-signifying behaviour is independent of ascertainable external stimulation; and so a biological rhythm is a mysterious essential of life.

Of course, it is a semantic error to call the organisms "clocks"; for they are clocks only to the observer who notes the regular form of their behaviour patterns. The organism is a clock-form only under experimental observation. If this error is not avoided, the observer searches for the position of the clock in the creature, the "endogenous mechanism". Though the misapprehension is implicitly denied by some of the authors, it is explicit in several statements. For example: "The generalization (concerning the regulation in time of physiological and biochemical processes) has gained an enormously greater impact through its statement in the form that organisms possess biological clocks—the subject of this symposium" (p. 87). Awareness of this error among biologists could save much time in their journey to the foundations of their problems, which are of universal and profound importance.

An awareness of rhythms in medicine, and especially in neurology, could help us to a more dynamic and flexible attitude to functions and their localisation (if any)—to the biography of disease rather than only to the statics of morbid anatomy, with the location of functions with the site of lesions. Medicine affords many opportunities for investigating rhythmic processes in health and disease, in psychological and physiological states. For example, in the sympathetic nervous system we have the nervous apparatus for that rhythmicity of organs and processes upon which the range and flexibility of the "voluntary" nervous system depends.

In the study of medicine the macrocosm of the star-orientated astronomers' Universe might be directly linked with the microcosmic intracellular tides. And Man, balanced halfway between them, might at last understand the nature of times and Time.

Pages in the History of Chest Surgery

RUDOLF NISSEN, M.D., professor of surgery, University of Basle; ROGER H. L. WILSON, M.B., assistant clinical professor of medicine, University of California School of Medicine, San Francisco. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 166. 60*s*.

BEFORE he died in 1830, Ephraim McDowell had reported eight successful ovariectomies and had established laparotomy as a perfectly feasible operation. Macewen, writing on brain abscesses in 1893, performed a like service for craniotomy. But for many years thereafter, diseases inside the chest remained beyond the reach of surgeons, who were deterred from opening that cavity by the difficulty they experienced in controlling the resultant pneumothorax, and in draining any infection which might ensue. Not until Sauerbruch (who at first operated in a bizarre vacuum chamber, from which the patient's head protruded) had indicated how these hazards might be avoided, could thoracic surgery advance very far.

Most of the papers described in this book, therefore, derive from comparatively recent work. (The earliest is dated 1881.) They are grouped under seven headings (such as heart surgery, anæsthesia, and the treatment of tuberculosis) and illustrated with photographs of their writers and often with a reproduction of one or two of the most significant pages of the actual paper.

Such an arrangement is attractive, but it has its limitations. The reduced facsimiles are sometimes hard to read, often in a foreign language, and always incomplete—on occasion, tantalisingly so. The book's title might have been better justified by a discussion of only a few papers, which could then have been reprinted at length. Nevertheless, what has been provided is an excellent outline account of the development of chest surgery, and one of the best bibliographies of its history that has yet been published.

The Structure of the Eye (*Proceedings of the Symposium held in April 1960 in association with the Seventh International Congress of Anatomists, New York.* New York and London: Academic Press. 1961. Pp. 570. 107*s*. 6*d*.).—This symposium must have been one of the most successful ever organised. Nearly all the papers published in this volume are important, well presented, and excellently illustrated. The growing importance of the electron microscope in the study of ocular structure is reflected in the fact that eighteen of the thirty-seven papers are based on its use. Since the symposium was held in association with an anatomical congress the accent is naturally on structure, but most of the authors are at least as interested in function, so that many of the papers are concerned with some relation between the two. Every part of the eye comes under discussion, but perhaps the most impressive set of contributions is the eight papers on the fine structure of the retinal receptors and the pigment epithelium. Dr. George K. Smelser is to be congratulated on gathering so many interesting and important contributions and in doing such a fine job of editing.

THE LANCET

LONDON 13 MAY 1961

Fibrocystic Disease and Sweat

SOME recent papers have been both cause and effect of a lively new interest in fibrocystic disease. The illness has been studied from the clinical, laboratory, and genetic angles; and its recent designation as a " community challenge " [1] reflects the shared impression that it is neither excessively rare nor wholly unmanageable. This welcome realisation has been accompanied by the first crop of bold generalisations and hastily interpreted statistics which are the common trappings of fashionable illnesses; and, though only confirmed scientific puritans would begrudge research pioneers their fun, fact and speculation must be disentangled.

Many workers have confirmed the remarkable findings of DARLING, DI SANT'AGNESE, PERERA, and ANDERSEN that children with fibrocystic disease have an abnormally high sweat-electrolyte concentration [2–4]; and " sweat-tests " of widely varying accuracy are now much used in the screening of patients with gastrointestinal and respiratory complaints. Unfortunately the limits of variation among healthy adults have never been clearly established; and recent work suggests that some of the statistical and diagnostic claims of the past few years may have been based on an imperfect appreciation of the normal range. Thus several groups of workers have reported abnormal sweat-electrolyte concentrations in a significant proportion of clinically normal parents and siblings of children with fibrocystic disease; and SMOLLER and HSIA have defined a range which they regard as characteristic of the heterozygous carrier state.[5] Others have recognised *formes frustes* in large numbers of adults with obscure chest symptoms, on the ground of sweat-electrolyte concentrations barely outside the childhood limits of normal; and we have already commented on KOCH's interesting work on the startling prevalence of sweat abnormalities in peptic-ulcer patients and their families.[6 7]

Three years ago ANDERSON and FREEMAN, while unable to detect any biochemical stigmata in healthy relatives of fibrocystic children, noted definite differences between the sweat-electrolyte concentrations of children and adults [8]; and their recent survey confirms this first impression.[9] Using intradermal injections of mecholyl hydrochloride to induce local sweating, they studied seven groups of people: 100 fully documented cases of fibrocystic disease, 100 healthy children (under 15 years), 100 children referred to hospital owing to respiratory symptoms, 61 clinically normal siblings and 100 clinically normal parents of fibrocystic children, 100 normal adults, and 47 normal adolescents (between 15 and 20 years). Like other workers they have found sweat-sodium estimation the simplest and most accurate measure of changes in sweat electrolytes; as little as 50 mg. sweat suffices for flame photometry. 95% of the known cases of fibrocystic disease had sweat-sodium concentrations higher than 60 mEq. per litre, and 61% had concentrations higher than 90 mEq per litre. In the remaining groups of children, however, the scatter was remarkably uniform—mostly below 40 mEq. per litre during the first year of life, rising to a fairly even distribution between 40 and 60 mEq. per litre by the 15th year. The pattern was also similar in the two groups of adults investigated, but the variations within each group were much wider. About 25% of both the normal controls and the potential carriers had sweat-sodium concentrations higher than 70 mEq. per litre; and in about 10% of each group the concentration exceeded 90 mEq. per litre. The scatter in adolescents was intermediate between that of children and adults; and advancing years after the age of 20 brought no further change.

These findings are important for several reasons. Though mecholyl-induced sweating may not be strictly comparable to heat-response sweating (the technique used by most American workers), they cast serious doubt on the distinct biochemical status of heterozygotes. The wide range of normal variations after puberty should also discourage over-diagnosis in clinical practice; and research-workers might be persuaded to review critically some of their earlier conclusions. There is no doubt, on the other hand, that outside a few forward-looking departments, under-diagnosis is still the greater danger. That some of the atypical manifestations of the syndrome (which include bronchial asthma at all ages) should be missed almost as a rule is perhaps not surprising; but even classical presentations are not recognised often and soon enough. A recent review of 6 cases of neonatal intestinal obstruction from the Harvard Medical School [10] should finally dispel the common belief that the sweat test cannot be applied to newborn infants. It is true that the method used by the Boston workers requires some skill and care; but in speed and accuracy it well repays the trouble spent on it. It is described as an " adaptation of the pilocarpine iontophoresis technique " first suggested by GIBSON and COOKE two years ago, and it eliminates both the danger of heat stress and the pain of injections.[11]

In the original method two modified electrocardiographic electrodes are applied to the forearm and a current of 2 mA is passed from the flexor to the extensor surface. Before the current is induced a few drops of pilocarpine solution are placed on a piece of filter paper inserted between the skin and the positive electrode; and a few millilitres of a sodium-bicarbonate solution are poured on the gauze-covered negative

1. Kulczycki, L. L., Macleod, K. I. E. *Publ. Hlth Rep., Wash.* 1961, **76,** 85.
2. Darling, R. C., Di Sant'Agnese, P. A., Perera, G. A., Andersen, D. H. *Amer. J. med. Sci.* 1953, **225,** 67.
3. *Lancet*, 1959, ii, 955.
4. Petersen, E. M. *J. Amer. med. Ass.* 1959, **171,** 1.
5. Smoller, M., Hsia, D.Y.-Y. *Amer. J. Dis. Child.* 1958, **96,** 685.
6. Koch, E. *Germ. med. Mon.* 1960, **5,** 40.
7. *Lancet*, 1960, i, 963.
8. Anderson, C. M., Freeman, M. *Med. J. Aust.* 1958, i, 419.
9. Anderson, C. M., Freeman, M. *Arch. Dis. Childh.* 1960, **35,** 581.
10. Elian, A., Shwachman, H., Hendren, W. H. *New Engl. J. Med.* 1961, **264,** 13.
11. Gibson, L. E., Cooke, R. E. *Pediatrics*, 1959, **23,** 545.

electrode. Pilocarpine iontophoresis for five minutes gives a good sweat response.

Foreknowledge of the diagnosis is of great value to the pædiatric surgeon. Ileostomy, which carries a prohibitive mortality in infants whose small-intestine contents are fluid, may be the operation of choice when the gut contains all-too-sticky meconium; or plans for a major operation may be abandoned in favour of a trial of pancreatic-enzyme replacement therapy either by mouth or through a gastrostomy. Whatever course is adopted, the sooner attention is directed to the chest the better. We are still not in a position to assess the full benefits of vigorous prophylaxis against respiratory infections (not only at the time of an operation but throughout childhood and adolescence); but of its value there is no longer any doubt. Less common but no less serious complications to be guarded against are salt depletion, heat exhaustion, and hepatic failure. In addition to the cases of obstruction, the Boston workers have investigated the sweat of 31 normal infants; and their data form a valuable supplement to those collected by ANDERSON and FREEMAN.

After the neonatal period respiratory infections, leading to bronchiectasis, pancreatic steatorrhœa, and biliary cirrhosis, are now recognised as "typical" manifestations of the syndrome, whereas the prevalence of peptic ulceration remains controversial. There are several theoretical reasons why ulcers might be expected to be common (such as the possible involvement of Brunner's glands and the inefficient neutralisation of gastric acid by abnormal pancreatic juices): yet SHWACHMAN and LEUBNER have gone so far as to say that they "have searched for the development of duodenal ulcers in some of their older patients and have not yet demonstrated this condition".[12] KOCH, on the other hand, has claimed that the coexistence of peptic ulceration and fibrocystic disease is at least 10 times more common than might be expected from chance alone [6 7]; and he is not without independent experimental and clinical support.[13 14] Whatever the statistical truth, a case recently described by ATERMAN [15] serves as a reminder that the possibility should at least be considered when fibrocystic patients present with gastrointestinal hæmorrhage. The chances are, of course, that the source of their bleeding is a ruptured gastro-œsophageal varix (secondary to portal hypertension); but, as in the 10-month-old infant reported by ATERMAN, necropsy may display a normal liver and a large chronic (as well as several acute) duodenal ulcers.

Only a step removed from the bedside, fibrocystic disease, with its hint that sweat may be the most unjustly neglected of body secretions, challenges the laboratory worker. Perspiration is said to account for two-thirds of genius; and yet its role as a biochemical regulator is little understood and probably undervalued. Sweat electrolytes are certainly under the influence of adrenocortical hormones; and a more detailed study of sweat chemistry may offer at least an alternative to urine analysis when primary disease of the kidney interferes with renal functions. It may also open up new therapeutic possibilities: LYBURN [16] has long maintained that, when sweating is induced by damp, very hot surroundings, the sweat-glands can function as accessory kidneys and that this "wet heat" is of value in the treatment of renal failure and some other conditions. Another striking prospect is that biochemical changes in sweat may reflect similar changes in more important but less accessible secretions. The high salt content of bronchial mucus in fibrocystic disease certainly predisposes to staphylococcal lung infections—staphylococci, unlike most other pathogens, flourish in a salt-rich medium—and similar changes in the chemical milieu may play a part in other respiratory diseases. Whether or not sweat can provide a clue to these and other diseases will require a good deal of perspiration and the whole of the remaining third of genius to answer.

12. Shwachman, H., Leubner, H. *in* Advances in Pediatrics (edited by S. Z. Levine); vol. VII. Chicago, 1955.
13. Poth, E. J., Fromm, S. M. *Sthwest. Med.* 1952, **33**, 16.
14. Andersen, D. H. *J. chron. Dis.* 1958, **7**, 58.
15. Aterman, K. *Amer. J. Dis. Child.* 1961, **101**, 210.

Progesterone and Uterine Cancer

THE observations of KELLY and BAKER [17] on the treatment of adenocarcinoma of the uterus with progestational agents are an important contribution to the growing volume of knowledge on the countering of malignant disease by alteration of the hormonal background. Prompted by the demonstrable regression, under œstrogen therapy, of malignant disease in the prostate and the breast, and by the considerable evidence that excessive œstrogen production is associated with endometrial cancer, they chose progestational agents for trial in advanced cases already treated unsuccessfully by surgery and radium. ELTON [18] has already reported that endometrial carcinoma appearing after the menopause often shows evidence of secretory activity and squamous metaplasia, suggesting that the tumour would respond to a progesterone-like substance; and the work of KISTNER [19] and others on the treatment of endometriosis with progestogens has demonstrated that long continued progestational treatment results in endometrial atrophy with or without production of decidual changes in the stroma.

KELLY and BAKER describe the outcome of treatment in 21 cases. The results are encouraging in that a distinct objective response took place in 6 cases, all with extensive local or disseminated recurrence, the remission ranging from nine months to four and a half years. In many of the other patients there was gratifying symptomatic relief, though without objective evidence of regression of the tumour.

The reason for this response is not at present clear: there was no evidence that during treatment the production of follicle-stimulating hormone was suppressed, or that œstrogen activity was altered; nor was there evidence that the progesterone was converted to other types of hormones, or that androgen activity was increased. Luteinising hormone was not measured, but SHERMAN and WOOLF [20] reported a drop in raised levels

16. Lyburn, E. F. St. J. *J. Physiol.* 1956, **134**, 207.
17. Kelly, R. M., Baker, W. H. *New Engl. J. Med.* 1961, **264**, 216.
18. Elton, N. W. *Amer. J. clin. Path.* 1942, **12**, 32.
19. Kistner, R. W. *Amer. J. Obstet. Gynec.* 1958, **75**, 264.
20. Sherman, A. I., Woolf, R. B. *ibid.* 1959, **77**, 233.

of this hormone in 4 patients with carcinoma of the endometrium treated for six weeks with progestogens. Direct action on the tumour, suggested by the work of KISTNER,[21] seems the most likely mechanism; but the inaccessibility of the recurrent lesions in most of the cases treated prevented any direct estimate of tissue response.

Perhaps the most notable aspect of this investigation is the contrast between the 6 cases in which the tumour clearly regressed and the 15 in which no regression took place. This suggests once again variations in the nature of malignant disease which we still cannot distinguish clinically or histologically. Further histochemical studies and comparison of the detailed structure in cases which respond to progestogens with that in cases which do not respond might prove fruitful, perhaps even yielding a clue to the fundamental problem of carcinogenesis.

Sodium Balance

SODIUM is important to the body both for its bulk action, which influences the tonicity and volume of the body-fluids, and for its specific function in nerves, muscles, kidneys, and probably all cells. There is an optimum concentration of sodium in the extracellular fluid (E.C.F.), but considerable divergence from this is compatible with survival and normal function. The simple test for red-blood-cell fragility demonstrates how these cells, at least, can survive and recover from immersion in a solution of osmolarity very different from that of plasma. The amount of sodium excreted is regulated by antidiuretic hormone (A.D.H.) and aldosterone; and this amount is conditioned by the intake. The exact mechanism underlying thirst is still unknown, despite recent advances concerning the regions of the central nervous system involved.[22] Thirst seems to depend as much on the concentration of electrolytes and water relative to each other as on the total quantities of the two.[23] Sensory endings must exist which sample body-fluids and transmit information to the hypothalamus, but what these endings are like is unknown. Indirect information about volume of body-fluids seems to be supplied by tension receptors in the blood-vessels. Theoretically, then, disorders of sodium and water balance can arise at many different sites.

In man the fluid intake is not governed simply by need: habit and social custom may determine the volume, which tends to exceed the need. Ordinarily this matters little since the kidneys quickly remove the surplus. But custom may lead to serious overloading and water intoxication; or intake may be reasonable but output inadequate because disease—for instance, congestive cardiac failure—has set in motion quite inappropriate processes of fluid or sodium retention.[24] In such cases the fluid retention is due not simply to poor renal circulation and pressure; it is connected with overfilling of the great veins and alterations in pulse-pressure at certain sites.

The evidence for the existence in the thorax of receptors sensitive to tension, with particular reference to volume regulation, is varied and circumstantial. For instance, in the waking state a passive change in posture from the recumbent to the vertical quickly reduces the urine flow and tends to reduce sodium excretion also.[25] The change in rate of urine flow is too rapid to depend on accumulation of extravascular fluid in the lower limbs. Moreover, functional reduction of blood-volume by pressure cuffs placed round the thighs has the same effect. Movement from the vertical to the recumbent position has the opposite effect, increasing urine volume and sodium excretion. Change of posture is certainly associated with alterations in renal hæmodynamics, but these may come to an end long before the change in excretion of sodium or water.[25] Attempts have been made to locate the site from which these reflexes arise, by inserting and inflating balloons in the great veins. Inflation induced a fall in venous pressure on the cardiac side of the balloon, and a reduction in sodium excretion which could not be correlated with changes in renal blood-pressure or flow.[26] Again, the rate of urine flow may be altered by positive or negative pressure breathing, the former leading to antidiuresis and the latter to diuresis.[27–29] It has been shown, too, that a hypotonic expansion of E.C.F. in recumbent water-loaded subjects increases urinary excretion of sodium, although the filtered load presented to the tubules actually decreases. Repetition of this experiment with the subject seated did not lead to increase in sodium excretion.[30] This is further indirect evidence that some mechanism in the upper half of the body is important. Probably there are regions between the great veins and the left atrium which respond to stretch (or its absence) and reflexly affect the regulation of both water and sodium excretion. These two systems, though linked, are nevertheless independent and can become individually disordered. This is not surprising, since it is fairly clear that the release of aldosterone and A.D.H., concerned respectively with the regulation of sodium and of water excretion by the kidney, is controlled by different parts of the central nervous system. The arrangement seems to be that the peripheral stimulus, whatever it is, is transmitted to the neurones making the hormones of the posterior part of the pituitary gland—i.e., the cells of the supraoptic and paraventricular nuclei of the hypothalamus—and at the same time to the region adjusting aldosterone liberation which is in and near the pineal gland.[31] There must be some pathway joining these two areas. Thus, in the regulation of sodium and water, trouble can arise at the peripheral sense-endings, in the aldosterone-regulating or antidiuretic-hormone-regulating parts of the central nervous system, or perhaps in the path linking the two regions.

"Cerebral salt wasting" was first demonstrated by CLAUDE BERNARD.[32] The condition is so called because

21. Kistner, R. W. *Cancer*, 1959, **12**, 1106.
22. Andersson, B., McCann, S. M. *Acta physiol. scand.* 1959, **33**, 333.
23. Welt, L. G., Seldin, D. W., Nelson, W. P., German, W. T., Peters, J. P. *Arch. intern. Med.* 1952, **90**, 355.
24. *Lancet*, Jan. 14, 1961, p. 92.
25. Strauss, M. B. Body Water in Man. London, 1957.
26. Farber, S. J., Becker, W. H., Eichna, L. W. *J. clin. Invest.* 1953, **32**, 1145.
27. Sieker, H. O., Gauer, O. H., Henry, J. P. *ibid.* 1954, **33**, 572.
28. Drury, D. R., Henry, J. P., Goodman, J. *ibid.* 1947, **26**, 945.
29. Baratz, R. A., Ingraham, R. C. *Amer. J. Physiol.* 1960, **198**, 565.
30. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., Rossmeissl, E. C. *J. clin. Invest.* 1952, **31**, 80.
31. Farrell, G. *Endocrinology*, 1959, **65**, 239.
32. Bernard, C. Leçons sur les propriétés physiologiques et les alterations pathologiques des liquides de l'organisme; vol. I. Paris, 1859.

it was thought to be always associated with a tumour or other lesion of the brain: for example, in the case described by CORT [33] the posterior part of the thalamus contained a glioma which distorted the posterior hypothalamus. The essence of this disorder is the appearance and persistence of an abnormally high urinary excretion of sodium combined with hyponatræmia; and in CORT's case there was some dehydration and hypotension. WELT et al.[23] suggested that perhaps cerebral salt wasting was due to inability of the proximal renal tubule to reabsorb sodium as it should. Sometimes, however, no renal disorder is detectable,[34] though the condition is invariably associated with a lesion of the thorax or central nervous system or of both.[35–37] In the patients described by SCHWARTZ et al.[35 36] mediastinal tumours were present; in ROBERTS's case [34] there was a bronchogenic carcinoma with no evidence of abnormality in hypothalamus, pituitary, kidneys, or adrenals. GOLDBERG and HANDLER [37] have described four further cases. In none was there œdema or ascites, nor were the patients dehydrated or hypertensive; but all had hyponatræmia with hypertonic urine and disorders of the central nervous system, such as disorientation, coma, hemiparesis, and ataxia. In one patient the neurological symptoms improved when the serum-sodium level was raised to normal. These workers and ROBERTS [34] found this was difficult to do, no matter how much sodium was given in the diet. Even an infusion of sodium-chloride solution raised the level very little since the additional sodium was rapidly excreted without an equivalent volume of water. The most effective remedy was severely to restrict the water intake without necessarily increasing the dietary sodium. Forced retention of sodium following administration of deoxycortone acetate worsened the condition since water was also retained [34]: this has been ascribed to an inappropriate production of antidiuretic hormone.[35 36] The rise in sodium excretion could be due to either an increase in glomerular filtration-rate or a decrease in aldosterone production.[38] Experimentally a state resembling cerebral salt wasting has been induced in healthy persons and dogs by administration of repeated doses of vasopressin,[39 40] which brings about water retention and subsequently increased loss of sodium—i.e., the sodium loss is secondary to the water retention. In these healthy subjects, as in the patients, sodium loss did not take place in the presence of dehydration. There was good evidence that the sodium-conserving mechanisms and all renal functions were unimpaired. In fact, the retention of water led to signs of water intoxication with no indication that excess vasopressin could cause œdema owing to simultaneous sodium retention. Glomerular filtration-rate rose somewhat, denoting that the tubules received an adequate volume of water and reabsorbed too much of it. The sodium loss occurred at a time when the serum concentration of this substance was low, and therefore it seemed unlikely that the serum concentration of sodium could be the stimulus which affected renal sodium conservation.[39] STEWART and ROURKE [41] induced sodium loss simply by acute overloading with water without administering antidiuretic hormone, and STRAUSS et al.[30] caused sodium loss by expanding the E.C.F. volume with hypotonic saline solution. These observations suggest that overexpansion of the fluid volume—and not antidiuretic hormone—is responsible for the sodium loss. This conclusion is supported by the observation that in adrenalectomised animals with diabetes insipidus the sodium pattern of the serum was normal, but that when water retention was induced by vasopressin hyponatræmia developed despite the absence of the adrenal glands.[42]

In cerebral salt wasting, then, the disorder may originate in overproduction of antidiuretic hormone, which leads to water retention, and this in turn to sodium loss. What brings about the overproduction of antidiuretic hormone? The cause may be direct irritation by a tumour, or indirect stimulation from cerebral vascular changes. Alternatively, the overproduction may be reflex in origin, the stimulus being any thoracic disease which distorts or destroys the so-called volume receptors.

33. Cort, J. H. *Lancet*, 1954, i, 752.
34. Roberts, H. J. *Ann. intern. Med.* 1959, **51**, 1420.
35. Schwartz, W. B., Bennett, W., Curelop, S., Bartter, F. C. *Amer. J. Med.* 1957, **23**, 529.
36. Schwartz, W. B., Tassel, D., Bartter, F. C. *New Engl. J. Med.* 1960, **262**, 743.
37. Goldberg, M., Handler, J. S. *ibid.* 1960, **263**, 1037.
38. Bartter, F. C., Liddle, G. W., Duncan, L. E., Jr., Barber, J. K., Delea, C. *J. clin. Invest.* 1956, **35**, 1306.
39. Leaf, A., Bartter, F. C., Santos, R. F., Wrong, O. *ibid.* 1953, **32**, 868.
40. Leaf, A., Mamby, A. R. *ibid.* 1959, **31**, 60.
41. Stewart, J. D., Rourke, G. M. *ibid.* 1942, **21**, 197.
42. Winter, C. A., Ingram, W. R., Gross, E. G. *Amer. J. Physiol.* 1939, **137**, 64.

Annotations

RHEUMATISM

"RHEUMATISM cripples in the largest number of cases and kills in the smallest. This very ability to cripple without killing now seems to put it in the lead of all other chronic diseases as of eminent social, economic and medical importance." This statement from the Annual Public Survey of the U.S.A. is reproduced by Dr. W. S. C. Copeman in the report of the Empire Rheumatism Council (see p. 1065). Another report, just issued by the Royal College of Physicians of London,[43] points out that "a treatment problem of such magnitude requires the cooperation of all branches of the medical service, and this is only beginning to take place".

Since the college's previous report, in 1951,[44] it has become more and more evident that, though the chronic rheumatic diseases predominantly affect the articular system, they also have important manifestations in the eyes, the skin, and the supporting framework of the internal organs. Responsibility for their management falls chiefly on the general practitioner, but they also demand attention from more physicians with wide knowlege and specialised training. The previous report suggested that, for research and teaching as well as for treatment, each region should have a special centre for the study of chronic rheumatic diseases. "This plan has proved fruitful to the limited extent to which it has been adopted"; but, of the centres now in existence (Bath and Bristol, Edinburgh, Hammersmith and Taplow, Manchester, Sheffield, and

43. Royal College of Physicians of London: Report of the committee of chronic rheumatic diseases. Approved in comitia on April 27, 1961.
44. See *Lancet*, 1951, ii, 219.

Stoke Mandeville), only the last two have been founded since 1950. Few consultant posts in rheumatology have been established in the National Health Service, and more than half the men and women trained in this country have gone overseas, where they can more easily get senior posts. In the U.S.A. since 1946 the number of centres receiving special research and training grants in rheumatology from money provided by Congress through the National Institutes of Health has risen from six to forty-five.

The college now concludes that some physicians should devote their whole time to this work; and its recommendation that the research and training centres should be directed by a " consultant rheumatologist " represents the—perhaps reluctant—recognition of a new specialty. Outside these regional centres, a large hospital or group may require a rheumatologist, but often its needs can be met by a physician with appropriate experience in rheumatology or physical medicine who gives only part of his time to rheumatic disorders. Whether a full specialist or not, such a man should concern himself mainly with unusual problems of diagnosis or treatment, and with clinical research: " prolonged supervision and treatment of patients in special clinics should . . . be avoided except when it is clearly necessary in the interests of individual patients or research ", and every effort should be made to encourage and support the care of the patients by their doctors at home. Alike in the general hospitals and in the special centres, orthopædic surgeons also have an essential part to play. In fact, the report is clearly an attempt to gain for rheumatic disorders some of the advantages of specialised study while promoting for the patient the readier use of whatever medical talents he may happen to stand in need of.

REOVIRUSES

Sabin [1] has recently described a new group of " reoviruses "—one of which was formerly called Echo 10. This virus has long seemed to be odd man out in the enterovirus family, being considerably larger (72 mμ instead of the approximately 30 mμ usual for enteroviruses). Some strains of the new group grow in chick embryos and all infect suckling mice, producing lesions in brain, heart, and liver. Stanley and his colleagues [2 3] described a virus isolated in 1953 from an Australian aborigine with a respiratory disease who later developed alopecia areata. They called this agent hepatoencephalitis virus and described an oily skin effect produced in suckling mice (and also jaundice, peritoneal exudate, ataxia, and fæces with a high fat content). Stanley [4] now describes tests showing that his virus is identical with reovirus type 3. Two strains of type-3 reovirus, Abney and Dearing, produced typical symptoms and lesions of hepatoencephalitis-virus infection in suckling mice. Hepatoencephalitis shared the following properties with reovirus: a common reovirus complement-fixing antigen; and ability to agglutinate human group-O red cells (hæmagglutination inhibition tests show that it is a type-3 reovirus). Neutralisation tests also show that serologically the virus is identical with reovirus type 3. The oily skin effect is not caused by neurotropic variants of reovirus type 3 which are selected by passage in chick embryos or tissue cultures. Stanley notes that the Amy strain of type-2 reovirus was isolated from a child suffering from steatorrhœa [5] and thinks that since reoviruses also cause fatty stools in mice they should be more fully investigated as a cause of steatorrhœa.

The difficulties of ascribing an ætiological role to these viruses is illustrated by the studies of Rosen et al.[6 7] in an orphanage in Washington, D.C. They found a high prevalence of type-1 and type-3 reovirus in two episodes of infection in the orphanage. The viruses may have caused a mild febrile disease, especially type 3, associated with coryza and diarrhœa, but the prevalence of these symptoms in the orphanage children who were not excreting reoviruses made this conclusion only tentative.

METRIC WEIGHTS AND MEASURES

SPEAKING in 1855, Charles Dickens reminded his fellow-countrymen that some Exchequer accounts continued to be recorded on notched sticks of elm wood (much as Robinson Crusoe kept his calendar) right up to the time of George III. Not until 1826 was the use of these tallies finally abolished. " In 1834 it was found that there was a considerable accumulation of them, and the question then arose, what was to be done with such worn-out, worm-eaten, rotten old bits of wood? The sticks were housed in Westminster and the order went out that they should be confidentially burned. It came to pass that they were burned in a stove in the House of Lords. The stove, overgorged with these preposterous bits of wood, set fire to the panelling: the panelling set fire to the House of Commons; the two Houses were reduced to ashes; architects were called in to build others; and we are now in the second million of the cost thereof." [8]

A recent broadsheet [9] from Political and Economic Planning suggests that our attitude to the decimal system is hardly less archaic. In terms of population, an overwhelming proportion of the countries of the world now use decimal systems of measurement and coinage. Four major countries have adopted metric systems during the past fifty years. None have adopted the imperial system, for there is no recorded instance of any country reverting after the metric system had been introduced. On the other hand, rather more of the world's trade is still conducted in terms of the imperial scales than the metric ones, but this is only because of the predominant positions, in commerce, of the Commonwealth and the United States considered together. And, even within the Commonwealth, a landslide towards decimalisation is now taking place. India introduced a decimalised coinage in 1957, and Pakistan followed suit this year. One of South Africa's last actions before leaving has been to change her currency; while official committees in Australia (1960) and New Zealand (1959) have urged similar changes. Another Government inquiry into the desirability of a decimal conversion is now in progress in Rhodesia.

There are, of course, some notable anomalies about the spread of the metric system. The aircraft of the U.S.S.R. are unique in having all-metric instruments, for the majority of aviation instruments read in imperial units, irrespective of the nationality of the men who are to operate them: even the Caravelle has some inch/pound components. Similar scales have been retained in the oil industry, because it is so much influenced by American

1. Sabin, A. B. *Science*, 1959, **130**, 1387.
2. Stanley, N. F., Dorman, D. C., Ponsford, J. *Aust. J. exp. Biol. med. Sci.* 1953, **31**, 147.
3. Stanley, N. F., Dorman, D. C., Ponsford, J. *ibid.* 1954, **32**, 543.
4. Stanley, N. F. *Nature, Lond.* 1961, **189**, 687.
5. Sabin, A. B. *Ann. N.Y. Acad. Sci.* 1956, **66**, 228.
6. Rosen, L., Hovis, J. F., Mastrota, F. M., Bell, J. A., Huebner, R. J. *Amer. J. Hyg.* 1960, **71**, 266.
7. Rosen, L., Hovis, J. F., Mastrota, F. M., Bell, J. A., Huebner, R. J. *ibid.* p. 258.
8. Fielding, K. J. Speeches of Dickens. London, 1960.
9. *Planning*, 1961, **27**, no. 449.

usage. And tradition still imposes on leather-workers everywhere the " square foot " unit.

Attempts have often been made during the past century to rationalise the British system of measurement. The most recent proposals are embodied in a Bill at present before the House of Lords. This provides for the abolition of some units (such as the rod, pole, or perch) and defines others (the pound and yard) in terms of metric equivalents, having a well-established, and more constant, value than the imperial standards now in use. A permanent committee to report on further changes that may be proposed is also amongst the Bill's stipulations. None of them would have any immediate effect on the medical profession: but the abolition of apothecaries' weights could take place not less than five years after the Bill became law.

In fact, doctors are likely to renounce the use of such weights even before then. When the next edition of the *British Pharmacopœia* appears, quantities will be expressed in it throughout as metric weights, save for certain traditional remedies such as Parrish's Food. The medical profession, with the opticians, electricians, and photographers of this country, have for long been amongst the principal supporters of the metric system.

MORTUARIES

THE Association of Clinical Pathologists [1] has drawn attention once again to the working conditions in mortuaries and postmortem rooms—a topic which was eloquently discussed in a letter from the Widdicombe File.[2] The Association seems to have ample justification for its criticisms of many places that are over a hundred years behind the times. Its plea for future standards of hygiene, efficiency, and decency is still very modest in comparison with the demands of other specialties. By the very nature of their work such services must be shielded from public gaze, but that is no reason why they should be neglected by the public purse.

A committee of the Association investigated current practice by circulating a questionary to pathologists in different parts of this country. The answers revealed extremely varied conditions—good, bad and indifferent. From that point the committee went on to define the ways in which improvements might be made towards reaching a standard which is obviously much overdue. A distinction was drawn between three types of need—those of general hospitals, teaching hospitals, and public mortuaries—but the fundamental principles are common to all.

Separate access for dead bodies and undertakers on the one hand, and for relatives on the other, is a matter mainly of common decency for the public and common sense for the architect. It can easily be incorporated in a new design but is often impossible in existing buildings, in which event intelligent and tactful control of the mixed traffic using a common entrance is needed.

The pathologists rightly stress the need for proper facilities for relatives to view a dead body. They favour a rather clinical atmosphere. Perhaps that might have to be tempered by some compromise towards the appearance of a chapel of rest. Many lay people feel repugnance at the idea of refrigerators and stainless-steel slabs: they recognise these as inevitable, but more human feelings may be called for to respect the distress of the bereaved.

1. *J. clin. Path.* 1961, **14**, 103.
2. *Lancet*, 1959, ii, 1081.

Nevertheless, behind the scenes, a refrigerator ought surely to be one of the main priorities for improving the older places. Beyond that, in the postmortem room, it is not unreasonable for any pathologist to expect cleanliness, good lighting, and effective ventilation: these have been demanded by law in most other workplaces for much less exacting and dangerous tasks. The Association explains in some detail what it would like to have in the way of rooms and furnishings and equipment—all very modest, very reasonable, and really self-evident to any architect or hospital management that brought a mind to bear on this essential service. The whole status of these places and their caretakers needs raising.

The Association commends the principle of joint use of mortuaries and postmortem rooms at hospitals by all who need them. The size may have to be related to the local need, but there is no excuse for their standards falling short of the best. There is still much to be done.

DENTAL ANÆSTHESIA AND HYPOXIA

DENTAL anæsthesia with nitrous oxide and oxygen is no longer regarded as an innocuous procedure; and no anæsthetist would now consider the technique of " secondary saturation ", once advocated by McKesson, by which the patient was rendered almost anoxic with nitrous oxide, and then resuscitated with pure oxygen before maintenance with gas and oxygen. Even transient hypoxia is now known to cause cerebral damage; and nitrous oxide is such a weak anæsthetic that the point at which anæsthesia passes into partial asphyxia is hard to determine.

Bourne [1–4] has done a great deal to draw attention to the hazards of gas-oxygen anæsthesia in the dental chair, in which the sitting position disposes the patient to syncope. The mortality may be low, but the incidence of cerebral damage is unknown. Schneider [5] showed many years ago that fainting may be caused by breathing mixtures containing a low percentage of oxygen; and in a patient already rendered unconscious by an anæsthetic, syncope (with its hypotension and consequent cerebral anoxia) may go unrecognised and unrelieved. All those who use gas-oxygen regularly have seen cases of delayed recovery, and Bourne [3] reckoned that there were at least 500 such cases a year in this country alone.

Keating [6] points out that very few anæsthetic machines will deliver a constant mixture of gases at different flow-rates and pressures. The patient and not the dial reading on the machine is admittedly the true guide to the depth of anæsthesia; but in a patient with a low hæmoglobin level, almost imperceptible cyanosis may denote dangerous hypoxia.

Adjuvants, such as halothane or trichloroethylene, may be used; but these are potent anæsthetics, not to be used lightly. Halothane, being a comparatively new agent, is still treated with respect; but trichloroethylene is now well known, and the fact that it should never be given with less than 20% oxygen tends to be forgotten.

A few years ago Mastert [7] recommended preoxygenation before dental anæsthesia—not primarily to avoid hypoxia, but rather to ensure more rapid induction and longer and smoother maintenance. He stated that, with

1. Bourne, J. G. *Brit. med. J.* 1954, i, 641.
2. Bourne, J. G. *Lancet*, 1955, ii, 295.
3. Bourne, J. G. *ibid.* 1957, ii, 499.
4. Bourne, J. G. Nitrous Oxide in Dentistry. London, 1960.
5. Schneider, E. C. *J. Amer. med. Ass.* 1918, **71**, 1384.
6. Keating, V. Anæsthetic Accidents. London, 1960.
7. Mastert, J. W. *Brit. med. J.* 1958, i, 502.

body-tissues fully oxygenated, an adjuvant was usually required. In 1951 Klock [8] showed that there was a plane of surgical anæsthesia between Guedel's stage I (analgesia) and stage II (excitement). This he called the stage of " amnalgesia ".

Roberts [9] has developed a technique combining those of Mastert and Klock. Twenty breaths of pure oxygen at 0–5 mm. Hg are followed by six to eight breaths of pure nitrous oxide. Twenty breaths of 12% oxygen/88% nitrous-oxide at 10 mm. Hg are next given. The operation may then be started. Roberts found that cyanosis does not occur and recovery is rapid. In a series of 127 unselected patients of all ages from 12 to 77, a success-rate of almost 85% was achieved.

The method seems to merit extended trial. A certain amount of experience is necessary to assess the correct level, but gaining this experience may pay dividends both in safety and in smoothness of the anæsthesia.

TUBERCULOSIS SURVEYS

THE diagnostic value of the tuberculin test increases as the prevalence of tuberculosis declines. In Great Britain a positive tuberculin reaction indicates infection with *Mycobacterium tuberculosis* acquired either naturally or through B.C.G. vaccination. So far, relatively few children under the age of 12 have been vaccinated; thus in this section of the community the tuberculin test remains an indicator of natural infection. As such, it can be used both to follow changes in the prevalence of tuberculosis and to discover unknown sources of infection in the adult population, through investigation of the contacts of infected children. If the test is repeated at intervals it becomes more valuable, for the shorter the period between infection and detection the greater chance of discovering the source.[10] But mass tuberculin-testing at short intervals requires staff, money, and organisation; and its value should perhaps be investigated more fully than it has been so far in this country before it is adopted as a general public-health measure.

A survey by Riddell [11] indicates what is practicable with present medical services and what results may be obtained. He surveyed 1530 children aged around $3^1/_2$ years of age in the county of Midlothian, repeating the test on as many as possible yearly for the next three years. Initially, 50 children had positive multiple-puncture tests; at the next two tests 11 more were found positive; and, at the final test, of 1319 previously negative children, 2 were positive. Thus, throughout the three-year period 63 infected children were discovered. All were X-rayed and kept under observation: in none did any other manifestation of tuberculosis develop. All available household and family contacts of these 63 children were fully investigated: only 1 previously unknown case of tuberculosis was discovered. The reward for so much work might be thought disappointing. But others have had different results. For instance, Griffith et al.[12] in Cardiff found active tuberculosis in 3 of 35 tuberculin-positive children under school age and in 7 of 1214 schoolchildren with strongly positive reactions. Moreover, of 1011 adult household contacts 13 were found to have active disease. In one London borough, Keeping and Cruickshank,[13] in a survey of 4800 children under 5 years old, recorded other evidence of tuberculosis in 19 of 35 infected children and 8 new cases of tuberculosis in adult contacts. Other surveys in the past few years have also yielded more new cases of disease among contacts than did the Midlothian survey.

Close comparison between different surveys is not possible. Different methods of skin-testing and of investigating positive reactors and contacts have been used; and large differences between the reported results may have arisen through variation in the thoroughness of the surveys and in the criteria for incriminating a particular individual as the source of infection. Some indication of the difficulties of tracing the source is evident from the Midlothian report. The proportion of infected children was much greater in the borough of Musselburgh than in the country districts. It seemed likely that in the borough some of the infection might have been milk-borne. 29 (71%) of the 41 children with positive tests drank milk obtained wholly or partly from one supplier; but there was no evidence of tuberculosis among the herd kept by this supplier for five years before the survey and throughout the three years it lasted. The possibility of contamination of the milk during bottling was examined; but investigation of the present and former dairy staff revealed no cases of tuberculosis. Furthermore, there was another complicating factor. In the area where the majority of the infected children lived there was a small sweetshop belonging to a known infectious person, who officially was not allowed to serve in the shop.

The difficulty of tracing sources of infection was emphasised by van Zwanenberg.[10] He established a tuberculin-test register in Ipswich to bring together the results of testing in school surveys, chest clinics, and hospitals. From this register he found 109 children whose skin had become tuberculin-sensitive between tests. 95 of these and their household contacts were carefully investigated; in only 31 was even a probable source of infection discovered. 28 of these were probably infected by 23 infectious individuals. A disturbing finding was that 16 of the 23 were already known to the chest clinic; only 7 new cases were found. In 2 instances the change in the tuberculin reaction of the child was the first indication of relapse of apparently healed disease in an adult. In another case the child's infection was finally attributed to the landlady of a boarding-house where she had stayed. Similar difficulties in tracing sources of infection were reported in the survey in London.[13] Among the contacts of the 35 infected children 8 new cases were found in adults; but in 13 further cases there had been contact with a known case of tuberculosis, although this was not known at the time by the parents or the chest clinic. In 1 case, for instance, an insurance agent recently found to have tuberculosis had regularly visited the house of one of the infected children during his work. In the remaining 14 of the 35 cases no source of infection was found.

Tuberculosis is declining in this country, but its eradication is highly improbable without something further being done. Present methods of detecting sources of infection are clearly ineffective, even when applied thoroughly in relatively small and stable populations. Possibly serial tuberculin-testing of children will eventually be found no more efficacious than other methods. But it should be more fully investigated on a large scale.

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9. Roberts, R. B. *Brit. dent. J.* 1961, **110**, 161.
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11. Riddell, J. *ibid.* 1961, **42**, 18.
12. Griffith, A. H., Bellamy, M. J., McFarlane, J. K. *ibid.* 1960, **41**, 233.
13. Keeping, J. A., Cruickshank, R. *ibid.* p. 239.

THE next session of the General Medical Council will open on Tuesday, May 30, at 2.15 P.M., when Sir DAVID CAMPBELL, the president, will deliver an address. The Disciplinary Committee will sit on Wednesday, May 31, at 2.15 P.M.

Needs and Beds

AN ORGANISATION FOR OUTPATIENT SURGERY

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MANY general surgical waiting-lists are so long that a patient with varicose veins or hernia may wait for two or three years to get into hospital. Often such patients are submitted to operation either as outpatients or on a short-stay basis. Farquharson (1955) has described an outpatient organisation designed to treat hernia under local anæsthesia, and he has used the technique on more than 600 patients (Mr. E. L. Farquharson, personal communication). But there is need for a better understanding of the scope and limitations of outpatient surgical treatment, and we here describe the formation of a service in a surgical unit of the Aberdeen Royal Infirmary.

Aberdeen Royal Infirmary is the only large hospital for general surgery in the north-east of Scotland, and the waiting-list of general surgical patients has grown steadily in the past ten years. At the end of 1959 the general waiting-list for the three surgical units (180 beds) was 1600. About a third of the patients on the list of the professorial surgical unit had varicose veins or herniæ. Because of a lengthy list of major surgery these patients had to wait from eighteen months to two years. Increase in beds or staff was not feasible, and it was therefore decided to explore the possibilities of their outpatient treatment by a special team.

The Outpatient Scheme

Criteria for Outpatient Treatment

It seemed necessary to satisfy three criteria:

1. That there is no absolute contraindication to the use of outpatient surgery for the condition under treatment. For varicose veins and hernia this can be established only by a carefully controlled trial; but the evidence so far is that, if early ambulation is accepted in management (Powers 1958), patients with these conditions derive no special benefit from a hospital bed. This conclusion is strengthened by experience in the United States Air Force (Gold 1958).

2. That the standard of surgery and anæsthesia should be the same as that used for inpatients. It was felt that general anæsthesia should be used, nct only to facilitate an unhurried relaxed technique of hernia repair but also to permit stripping of varicose veins.

3. That preoperative examination and assessment should be at least as complete as for the inpatient. This requires an adequate outpatient clinic in which anæsthetist and surgeon can see the patient together, arrange investigations, and advise the patient about the form his treatment is to take (Sutherland and Horsfall 1961).

In addition to these surgical criteria it is necessary to select appropriate patients, to secure a measure of post-operative supervision either from the hospital organisation or from the patient's own doctor, and, if necessary, to make arrangements with the almoner, the district nurse, and such ancillary departments as the ambulance service.

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Selection of Patients

All 212 patients on the waiting-list with varicose veins or hernia were reviewed. Those over the age of seventy or living more than 10 miles from the hospital were arbitrarily excluded. The 182 who remained were then invited to attend a special clinic (having had a mass miniature X-ray film of the chest) so that their suitability for an outpatient operation might be assessed.

At the clinic the patient was examined by an anæsthetist and surgeon together:

The results of this examination (described by Sutherland and Horsfall 1961) led to the rejection of 11 patients on medical grounds. Outpatient venography was performed when the standard tourniquet tests for varicose veins revealed below-knee incompetence; 2 patients were consequently rejected when it was established that very extensive below-knee operations were required. An effort was made to assess social circumstances, but rigid criteria for selection or rejection on social grounds were not laid down; in fact only 5 patients whose domestic circumstances were clearly quite unsuitable were rejected.

Those accepted were found to come from a very wide variety of homes and social classes. 2 patients who were considered especially suitable for outpatient treatment declined: 1 had unusually difficult home circumstances of which the team was unaware at first, and 1 was unwilling to burden his wife with extra work.

Thus, only 18 of the first 182 patients (10%) were finally excluded from outpatient treatment. The average age of those accepted was forty, with a range of fourteen to sixty-nine. These patients were given an appointment to attend the ward for operation, and provided with instructions about preoperative preparation.

The details of the scheme were fully explained to each patient, and when they attended for interview it was arranged that they shared accommodation in the waiting-room with those returning for removal of sutures.

All the operations were done by one surgeon (F. O. S.) with the same team of two anæsthetists. A special theatre session was devoted to outpatient operations on the understanding that the routine lists would be shortened. This required much effort on the part of the theatre staff, but in fact it has spread their operating load more evenly.

Usually 4 patients were operated upon at a session, but this number was adjusted if either difficult or simple procedures were undertaken. A standard anæsthetic technique was used although the preoperative and postoperative medication varied (Sutherland and Horsfall 1961). The herniæ were repaired by a Bassini operation with Halsted-Tanner relaxation incisions in the rectus sheath. Treatment of the varicose veins varied with the clinical and venographic findings: isolated long-saphenous incompetence was treated with unilateral or bilateral high-saphenous ligation, usually with stripping; the short-saphenous vein was ligated but not stripped if its incompetence had been demonstrated; more complex forms of below-knee incompetence were dealt with by selective ligation on the basis of the venographic findings.

After operation each patient recovered consciousness on a bed in the general ward, and after five to eight hours he was taken home by special ambulance. He was visited by a member of the team next day, and was asked to report to the outpatient clinic after a week for removal of sutures, and review.

Cooperation with General Practitioners

An apparently somewhat arbitrary selection of patients for surgery might have given the impression that the hospital was abdicating its responsibility and expecting the general practitioner to increase the burden of his work.

TABLE I—OPERATIONS PERFORMED IN 166 PATIENTS

Operation	Males	Females	Total
Unilateral inguinal hernia *	36	2	38
Bilateral " "	9	..	9
Femoral hernia	2	3	5
Unilateral varicose veins	15	51	66
Bilateral " "	14	32	46
Inguinal hernia and varicose veins	2	..	2
Totals	78	88	166

* 36 oblique; 13 direct; 3 recurrent oblique; 2 recurrent direct; 2 saddle.

Accordingly, each doctor was asked by letter if he would agree to his patient being operated upon as an outpatient, provided arrangements for care were centred on the hospital. However, it soon became clear that this was unsatisfactory and that the doctors were more than willing to share in the care of their patients. Each doctor who is having a patient operated upon by the organisation for the first time is now contacted by personal letter and occasionally by telephone.

Results

166 patients have so far been operated upon—78 men and 88 women (tables I and II). Early ambulation was encouraged, and most patients were up for toilet purposes either on the evening of operation or next day. The majority, but not all, were fully ambulant by the seventh day after operation, though 11 were, at their own or their doctor's request, provided with ambulance transport for their first return visit at seven days. At this visit or later the patients were asked for their views on the success of the scheme, and this was also assessed independently in about two-thirds of them by a medical student who visited their homes. Because patients are often anxious not to offend their surgeons they may be biased in their replies, but we hope that these answers are reliable:

151 patients preferred outpatient treatment (of these 83 had had experience of inpatient treatment); 8 would have liked to have had the first night in hospital; 4 had no preference; 2 would have liked full inpatient treatment; and 1, although satisfied with the outpatient organisation, felt she was a burden on her family during her early convalescence.

TABLE II—METHODS OF TREATMENT OF VARICOSE VEINS

Operation	No. of legs
High-saphenous ligation	8
High-saphenous ligation and stripping	133
Re-exploration and high ligation with or without stripping	5
High-saphenous ligation and below-knee procedure	12
Total	158

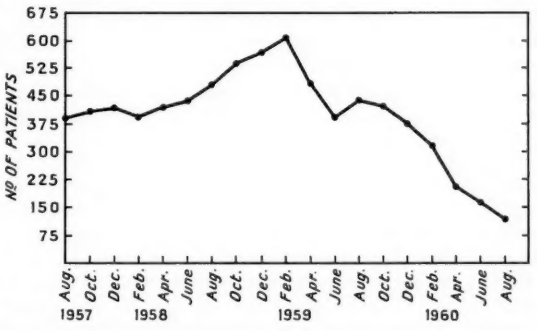
The effect of the outpatient organisation upon the surgical waiting-list of the unit (to which new cases are added steadily) is shown in the figure.

The initial reduction in the first six months of 1959 is the result of an effort to reduce the list by increasing the turnover of inpatients—an effort which could not be sustained. The fall is much greater than the total of outpatients treated because the beds freed can be used to admit other patients, provided theatre time is available. In particular, the very minor surgery which accumulates excessively on many waiting-lists can be worked off. Already our waiting time has fallen from two years to three months for minor inpatient surgery. We are now trying to control the numbers on the waiting-list more accurately so that the present fluctuations and the consequent wide variations in waiting time are reduced. Ultimately it may be possible to apply a " control chart " of the type used in industry to this problem, basing it on the ideal figure of a waiting-list no greater than the number of beds available.

Complications and Difficulties

Postoperative pulmonary collapse or major chest infection, urinary retention, and wound infection have all been conspicuous by their absence. A matched series of controls has not yet been completed because of shortage of beds and the difficulty of keeping in hospital patients who see their neighbours treated as outpatients; but since the scheme was started there have been 2 wound infections and 1 case of urinary retention among 80 patients under seventy with herniæ and varicose veins who were treated as inpatients.

Management postoperatively of pain, minor respiratory complications, and vomiting are discussed by Sutherland and Horsfall (1961). The 2 wound hæmatomata were both in patients undergoing second operations—one for varicose veins, the other for hernia—and both collections resolved spontaneously. Post-operative vomiting, at first frequent, was much reduced by the routine use of perphenazine before and after operation.



The effect of outpatient surgery on the waiting-list of the professorial surgical unit.

Discussion

This project was begun primarily in an attempt to break the never-ending circle of too many patients for too few beds. We felt some trepidation about the effects, both surgical and social, of stripping varicose veins and repairing herniæ on an outpatient basis, but these fears have proved groundless. We did not at first expect benefits beyond those evident in our waiting-list statistics. However, it has become apparent that positive advantages are to be gained: some of these have already been mentioned by Farquharson (1955), but we have encountered others:

First, for many people, the hospital is still a place in which they would rather not stay: out-of-date buildings, noise, and the proximity of seriously ill patients contribute to this dislike. It came as a relief to most patients not only to learn that their condition was sufficiently minor to warrant their return home but also to find that they could sleep in their own beds and convalesce in their own environment without the need to submit to a somewhat irksome discipline. As the practice has grown, the initial fear of going home has gone, and many patients now ask spontaneously for outpatient treatment. Women in particular are glad to return home where they can at least exercise control over the family, even though for a few days they cannot take an active part in the housework. A further small but not unimportant point is that most women feel impelled to buy new night clothes and toilet accessories before going into hospital, but are prepared to economise if treated as outpatients. The contrary view that the housewife should have a short holiday from her family while undergoing an operation is not supported by our experience.

Secondly, reduction in a long waiting-list has a very favourable effect on the morale of the unit.

Thirdly, the scheme has helped slightly to integrate general practitioners into the hospital service. Most doctors are clearly pleased to share in the day-to-day management of their patients, particularly if this means a much shorter wait for hospital treatment.

Finally, there will probably be some ultimate reduction in the cost of treatment of an individual patient. At the moment, of course, the cost of a hospital bed is unchanged because an empty bed is immediately filled from the waiting-list. Indeed, the cost to a patient is slightly more in that he no longer avails himself of the hotel facilities of the hospital. The effort of the surgical unit must be entered partly on the credit and partly on the debit side. A scheme of this kind is stimulating, and the standard of care is almost certainly increased: nevertheless a great deal of time and energy must be expended if a good service is to be provided. In particular it may prove difficult to find theatre time, but the increased efficiency and reduction of the waiting-list seem to justify some curtailment of inpatient lists in favour of a steady outpatient turnover.

The implications of continuing a scheme of this kind are many. The aim is to make better use of the expensive hospital bed as suggested by Stallworthy (1960) and others (Ralston 1960), and if, as we hope, it is not detrimental to the patient in terms of results, then it may well influence hospital design. In particular, more theatre accommodation will be necessary in proportion to the number of beds. From the reaction of the patients already treated one would expect that, with the rising standard of living, the demand and scope for outpatient surgery will increase, in that social pressures for privacy cannot be adequately provided for some years at least. We do not yet know how much the distance from the hospital may be increased, but this has already been extended in a few cases up to 30 miles. Nor are the long-term surgical results yet known. In the varicose-vein group it is reasonable to assume that they will be comparable to those for inpatient treatment. The outlook for hernia recurrence is less certain, but none has taken place so far.

Summary

An organisation for the satisfactory conduct of outpatient surgery has been devised.

166 patients have had operations for hernia or varicose veins without incident, and of these 151 preferred outpatient treatment to hospital admission.

Adoption of schemes of this kind might do much to relieve the unrelenting pressure on surgical beds.

We could not have attempted the work described without unstinting cooperation from our nursing, surgical, and secretarial colleagues. The general practitioners of Aberdeen and its environs have been most forbearing when, particularly in its early stages, the organisation did not function as smoothly as it should. Dr. John Young, of the mass miniature radiography service, and Dr. Roy Weir, of the department of social medicine, gave us much help. Messrs. Allen & Hanburys provided the perphenazine and gave financial assistance to one of us (F. O. S.). Dr. Lister Horsfall and Dr. John Sutherland gave all the anæsthetics with great skill.

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ANÆSTHESIA FOR THE OUTPATIENT TREATMENT OF HERNIA AND VARICOSE VEINS

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THE outpatient management of 166 patients with varicose veins or herniæ has been described by Stephens and Dudley (1961). We are here concerned with the anæsthetic technique and postoperative findings in 140 of these cases, the first 26 having served to establish and standardise methods so that comparison of results of anæsthesia would be possible.

Preoperative Assessment and Selection

Each patient was examined in a special clinic by the surgeon and anæsthetist together, but the anæsthetist was mainly responsible for the general physical assessment, which included routine blood-pressure records and analysis of the urine.

TABLE I—POSTOPERATIVE ANALGESIA REQUIREMENTS IN RELATION TO PREMEDICATION

No. of patients	Premedication	No. of patients having sonalgin within 24 hours	No. of patients having additional analgesics within 24 hours
65	Papaveretum 20 mg. Atropine 0·6 mg.	53	13
25	Papaveretum 20 mg. Atropine 0·6 mg. (perphenazine 5 mg. postoperatively)	25	1
50	Perphenazine 5 mg. (repeated 4–5 hours postoperatively)	50	0

Blood studies, peak expiratory flow-rates (Wright and McKerrow 1959), and electrocardiography were done when indicated. A special anæsthetic outpatient form was used and incorporated in the patient's case-records, and the premedication, operative details, and postoperative sedation were later entered on its reverse side. Patients were rejected for outpatient surgery only after consideration of all the physical findings and a routine miniature X-ray film of the chest, supplemented, if necessary, by a full-size plate. The decision was undertaken by both surgeon and anæsthetist rather than by either alone.

11 patients were regarded as definitely unsuited for outpatient surgery on medical grounds:

Undetected mitral stenosis	2
Previous coronary occlusion	1
Large emphysematous bulla	2
Active pulmonary tuberculosis	1
Aneurysm of ascending aorta	1
Asthma, chronic bronchitis, and effort dyspnœa	1
Severe urinary difficulty	3
Total	11

Numerous other abnormal findings were revealed either by physical examination or chest X-ray:

Chronic bronchitis and emphysema	10
Old or healed pulmonary tuberculosis	9
Other abnormalities on chest X-ray	7
Peptic ulcer	8
Hypertension (diastolic >100); angina	21
Cardiac murmurs	5
Gross obesity	8
Urinary difficulty	2
Miscellaneous	8
Total	78

This shows the value of routine radiography. Perhaps the greater age of our patients explains why we found more abnormalities on chest X-ray than were previously reported by Loder (1955).

Premedication

Because simplicity was the aim of the anæsthesia, heavy premedication was avoided. We used at first papaveretum 20 mg. and atropine 0·6 mg. by intramuscular injection an hour before operation, but we abandoned this after the

first 90 cases, because we thought the papaveretum was an important cause of nausea and vomiting. The last 50 cases were given standard premedication of perphenazine 5 mg. by intramuscular injection one hour preoperatively because of its mild sedative and powerful anti-emetic effects. Atropine was omitted in an attempt to collect information about its influence on postoperative chest complications, but this study is not yet complete and will be reported separately. The patients given perphenazine premedication were not as drowsy as those who received papaveretum, but they were relaxed and free from anxiety on arrival in the anæsthetic room; indeed some were mildly euphoric.

Anæsthetic Technique

It seemed desirable in outpatients to avoid endotracheal intubation and to try to ensure a speedy recovery with as little postoperative nausea and vomiting as possible. With these requirements in mind, anæsthesia was induced with a dose of 2·5% thiopentone sodium based upon age, sex, weight, and body build, and sufficient to produce sleep. The amount never exceeded 500 mg. Maintenance was with a 50% nitrous-oxide/oxygen mixture supplemented by halothane. The flow-rate was high at first to eliminate the nitrogen in the alveolar air, and this was later reduced to a 3-litre flow through a circle absorber with an intentional leak. The halothane vaporiser (B.O.G. pattern) was outside the circle system. A well-fitting facepiece was used, and an oral airway was inserted as soon as it could be tolerated.

TABLE II—EFFECT OF PERPHENAZINE ON POSTOPERATIVE NAUSEA AND VOMITING

No. of patients	Premedication	No. of patients having perphenazine 5 mg. 4–5 hours postoperatively	Incidence of nausea and/or vomiting postoperatively
65	Papaveretum 20 mg. Atropine 0·6 mg.	0	26%
25	Papaveretum 20 mg. Atropine 0·6 mg.	25	28%
50	Perphenazine 5 mg.	50	8%

Throughout the operation routine records were made of pulse-rate and blood-pressure. A reduction in blood-pressure of more than 22% was not observed in any patient; but one man, whose premedication was with papaveretum and atropine, developed a bradycardia of less than 40 per minute, and he was therefore given additional atropine. Although atropine was not used in the perphenazine group 2 patients, both over fifty, developed pulsus bigeminus; in each, normal rhythm was restored when the halothane concentration was reduced. The number of patients who had no atropine is, of course, small, but should this be advantageous in preventing chest complications, the halothane seems to carry little risk.

Postoperative Medication

Whatever the premedication, recovery of consciousness was rapid, and discomfort was slight. For this reason, and to avoid using dangerous drugs in the home, postoperative sedation was limited, apart from perphenazine, to a compound tablet containing butobarbitone, phenacetin, and codeine phosphate (' Sonalgin '). Most patients had two of these tablets on the first night, and few required additional analgesics during the first twenty-four hours after operation if they had had pherphenazine (table I). In the patients undergoing hernia repair, this regime was usually adequate though occasionally the night after operation was rather disturbed. But complaints were few, this being accepted as part of the surgical adventure. Some patients were drowsy for 24 hours but most were able to enjoy light meals the day after operation. Almost without exception the patients were surprised at how slight was their discomfort.

TABLE III—EFFECT OF THIOPENTONE SODIUM ON POSTOPERATIVE NAUSEA AND VOMITING

Dose of thiopentone sodium	No. of patients	No. with nausea and vomiting
Less than 400 mg.	53	19 (*36%*)
400 mg. or more	87	9 (*10%*)

Nausea and Vomiting

A patient was regarded as having vomited if retching produced 30 ml. or more of stomach contents. Among our first 65 patients, nausea and vomiting was frequent (table II), and this usually happened five or six hours after operation, coinciding with preparation for the patient's return home. Consequently, 25 patients who had had papaveretum and atropine premedication were given perphenazine 5 mg. intramuscularly four to five hours after operation to cover this period of movement and transportation. The incidence was little changed, but the symptoms were much less severe. 50 further cases were then given premedication with perphenazine alone, and a second dose of 5 mg. was administered four to five hours after operation. This reduced the incidence of nausea and vomiting to 8%—i.e., 4 patients in the 50 so treated, of whom only 1 vomited.

Factors other than premedication which might influence nausea and vomiting were also considered.

In this series the incidence was greater in patients who had had less than 400 mg. of thiopentone sodium than in those who had had 400 mg. or more (table III). Sex was relevant, vomiting being significantly more common in females (table IV). Vomiting was more often associated with ligation and stripping of varicose veins than with hernia repair, but the number of women presenting for treatment of varicose veins far exceeded the number of men. Finally, although the numbers are too small to show significant differences in these symptoms in the various age-groups, the general trend suggests a decreasing incidence with advancing years. This concurs with the experience of Davies (1960) at East Grinstead.

Respiratory Complications

No attempt was made to stop patients smoking. Our criteria for the presence of respiratory complications were: localised chest signs, rise of temperature and pulse-rate, and a productive cough. Of the 140 consecutive patients adequately studied, only 6 developed one or more of these signs. In each case this happened during the winter months, and the patients were all men who smoked but who had shown no clinical or radiological evidence of chest disease at the preoperative examination. 4 of the 6 had herniæ repaired, and the other 2 had varicose veins stripped. All had recovered completely when seen a week later, after deep-breathing exercises and instruction on coughing while supporting their wound. This regime was used from the outset in 8 patients, who, from history

TABLE IV—INCIDENCE OF NAUSEA AND VOMITING IN RELATION TO SEX

Sex	No.	Nausea	Nausea and vomiting
Males	67	0	3
Females ..	73	8	17
Totals ..	140	8	20

and clinical examination, were diagnosed before operation as chronic bronchitics; none showed any evidence of respiratory complications after operation.

Discussion

As anæsthetists we were gratified to learn from the patients at follow-up that they were relieved to go home in the evening after their operation. Expressions such as " hospital is all right for ' big operations ', but it is much nicer to be going home when recovering from small things like this " were common. This seems to have contributed to the surprising degree of comfort which these patients experienced. Both surgeons and anæsthetists tried to make light of the postoperative pain which would be experienced and to emphasise that analgesics would be given to ensure a good night's sleep. Thus encouraged, most patients were well content with their first night after operation.

Our anæsthetic technique proved very satisfactory, and when combined with perphenazine before and after operation it was free from difficulties or complications. Indeed, some patients who experienced only nausea had previously vomited for twenty-four hours or more after operation.

In the past an anæsthetist has not infrequently been confronted with an outpatient whom he has seen for the first time only a short while before operation. This is neither satisfactory nor safe. A proper organisation, centred on an outpatient clinic in which all the appropriate investigations can be undertaken or initiated, is a safeguard for the patient and a stimulus to the anæsthetist. We feel strongly that this is why most of our patients were successfully managed.

Summary

A series of 140 patients agreed to undergo surgery for the repair of hernia or the cure of varicose veins without being admitted to hospital. Their selection and anæsthetic management is described.

The system of preoperative assessment in an outpatient clinic, and of postoperative management in the patient's home, has proved successful and has reduced a large waiting-list, thus liberating beds for more serious and urgent cases.

We wish to thank the director of the department of anæsthetics, Dr. W. N. Rollason, for his guidance, help, and encouragement throughout this study and in the preparation of this paper. Our thanks are also due to our two surgical colleagues, Mr. F. O. Stephens and Mr. H. A. F. Dudley, and to the general practitioners, nurses, and patients who participated in this study.

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Special Articles

CHROMOSOMES FOR BEGINNERS

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In this subject of human chromosomal anomalies we are all beginners. It is so new that even the old hands were new themselves two years ago. It has travelled so fast that it has shot past the average reader before he has had time to notice that it has begun to move, and he begins already to be frightened of it. This is a pity: the chromosomes are still essentially a very simple matter.

Classical genetics as applied to medicine demands a high level of conceptual thinking. It is a little like medieval medicine, deducing the nature of disease without ever looking inside the patient; it relies on imperfect analogies with conditions in plants and insects, and on a very complex and largely mathematical system of deduction, to arrive at a purely notional model of what goes on at the chromosome level (this is not to decry its necessity or its truth, only to explain why the average brain finds it so difficult). The new methods may be still extremely crude: we are like a student watching a postmortem from the back benches of a large theatre, able to recognise that the liver is grossly enlarged or one kidney missing. But at least we can now really *see* something. They help us to understand only a corner of the field, but into that corner they shine a refreshing beam of good honest morbid anatomy, something tangible, unequivocal, simple to understand. It is well worth making a small effort to catch up with the main lines of discovery.

I have been charged with the task of making the subject intelligible to those who missed the beginning of the story. I propose to be as dogmatic as possible. I shall try to avoid saying anything demonstrably untrue; but to those who know the subject in much greater depth than I do, I hope I may be allowed to say firmly that this account is not intended for them.

The Method

IDENTIFYING CHROMOSOMES

Let us take the bull by the horns and begin with one of those exasperating pictures with which the pages of *The Lancet* have been so freely littered recently, and which are said to look like masses of squashed spiders. (Fig. 1.)

This is a normal mitosis—a mitosis skilfully coaxed, doctored, and stretched so that its chromosomes lie flat and separate; and stained and photographed so that everything except chromosomes is eliminated. (This is by no means as good a preparation as is possible, but it is sufficient for most purposes.)

Each of the little spiders is a chromosome (not, as you might easily suppose at first sight, a pair of chromosomes). Count them: you will find there are 46—the normal number. At first they look very much alike, but even a little attention will show that they differ a great deal in length. This is not just random variation. This will become more obvious if one examines the other point of distinction, the position of the *centromere*.

Before mitosis starts, the chromosomes have already nearly split into two chromatids, but they remain adherent at the centromere. At the crucial moment of division, the pull of the spindle splits the centromere, the chromatids separate to travel into the daughter cells and become its chromosomes in their turn. In the mitosis at which we are looking, the presence of colchicine in the brew has resulted in absence of the spindle, so that the centromere remains unsplit and the two chromatids remain tied together. The two are always exactly alike (apart from accidental bending in preparation) and whatever happens to the chromosome, it is always symmetrical. When one speaks of the " short arm " of a chromosome, one means *both* of the two shorter legs of the spider, and one tends to speak of them as though they were still fused together.

Fig. 1—A normal human mitosis, from a blood-cell culture prepared for chromosome analysis.

Note that each of the 46 bodies present, though apparently double, is a single chromosome, not a pair. An example of a chromosome pair, readily recognisable as such, is offered by the two large chromosomes lying at right angles to each other in the upper left corner: these are pair no. 2—their nearness is purely fortuitous.

The centromere does not stain with the usual chromosome stains, and hence appears as a gap in the middle of the spider. The ratio between the lengths of the two arms separated by the centromere is constant for any one chromosome pair, and this is of great importance in identification.

If we arrange the chromosomes strictly in order of length, as has been done in fig. 2, the use of this begins to be obvious. (Fig. 2 is based on the official Denver nomenclature: note that only one of each pair is represented.) Most chromosomes, especially the big group of medium size, have the short arm about half the length of the long arm; but some have the two arms more nearly equal (1, 3, 16, 19, 20) and some are "acrocentric" with the centromere near the end (13, 14, 15, 21, 22, Y, and to a lesser extent, 4 and 5). The acrocentrics are the easiest of all to pick out. The group of middle-sized acrocentrics, 13–15, is a specially important landmark. Using fig. 3 as a guide, you should have no difficulty in picking them out in fig. 1.

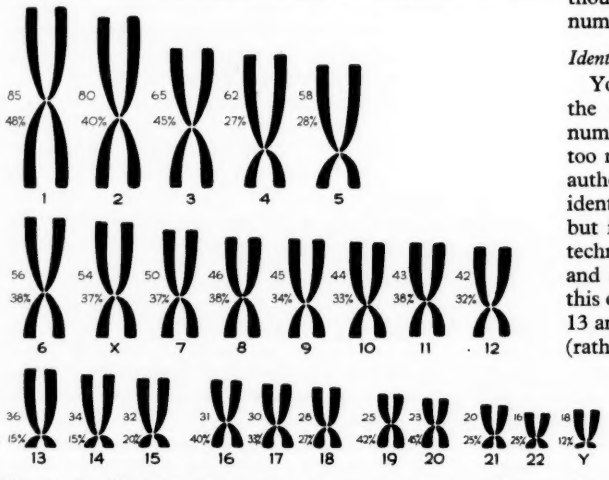


Fig. 2—An idealised chromosome set, numbered according to the internationally agreed Denver system.

Note that only one of each pair is represented. The small figures beside each chromosome indicate approximately the relative length of the whole chromosome, and the proportion of the total length occupied by the short arm.

The very smallest chromosomes are also acrocentric, though, especially in a photograph, it may be hard to see this clearly. But the next larger group (pairs 19 and 20) have definitely central centromeres and look like small fat starfish, and in consequence the smallest group is easy to separate. Since the Y belongs to it, there are five small acrocentrics in the normal male but only four in the female. Would it seem too much like a parlour game to suggest that you use this method to determine the sex of fig. 1?

The Chromosome Groups

Carrying on with this process, the chromosomes arrange themselves into well-defined groups (fig. 4). According to the Denver system, these are simply called group 1–3, group 4–5, group 6–12, group 13–15, group 16–18, group 19–20, and group 21–22 (less unimaginative names are used for the groups also, but as no two workers seem to use the same names it is better to stick to the simple numbers). With even a moderately good preparation, analysis of the chromosomes into these groups should be easy and unequivocal, and it should always be possible to say to which group a missing or an extra chromosome belongs—though of course it is always a good thing to have a fair number of mitoses to analyse to check the findings.

Fig. 3—The six chromosomes of group 13-15 from fig. 1.

The group is very characteristic, but it is hardly possible (certainly not in this preparation) to separate them into three pairs. The apparent attachment of three of them together by their short arms is in this case not a matter of chance, but is common with the acrocentric chromosomes and perhaps reflects their association with the nucleolus—perhaps also it is a source of anomalies.

Identification of Individual Pairs

You will find that in most cases published recently all the chromosomes have been neatly paired off and numbered according to the Denver system. Do not be too much discouraged if you find it hard to see how the authors have separated off the pairs. Just how complete identification can be is a matter of considerable dispute, but it is unlikely that even with the best of present-day techniques it can extend to all the pairs. Pairs 1, 2, 3, 16, and (often) the Y are certainly identifiable, but beyond this one gets into trouble. It used to be thought that pairs 13 and 21 could be identified by the presence of satellites (rather ill-named irregular whiskery excrescences on the short arm) but it seems now that these are characteristic of the acrocentrics generally rather than of individual pairs.

Take, for instance, pairs 4 and 5. It is easy to identify them as a group of four, for they have a much shorter short arm than anything at all near them in size. But to separate the two pairs is another matter. There is some random variation of chromosome length (demonstrable, for instance,

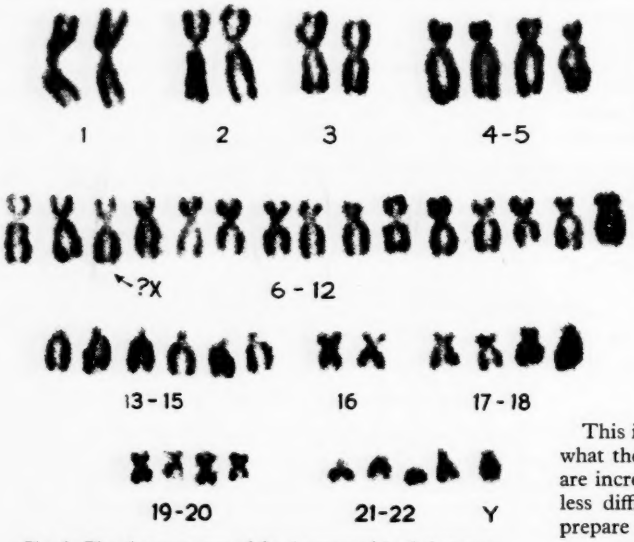


Fig. 4—The chromosomes of fig. 1 arranged in their groups.
Within the groups they have been arranged as far as possible in order of length, but have not been paired off. The presence of five small acrocentrics and of only fifteen chromosomes in group 6–12 show that this is a male, although identification of the X is quite arbitrary and of the Y in this case not absolute.

between the two members of pair 1 in many individual mitoses) and this can easily be greater than the difference between the mean size of the two pairs. Perhaps in an occasional exceptionally good mitosis we may think we can make out one pair a little smaller than the other. But we can never be quite certain. So, for instance, if we had an extra chromosome in the group we should have great difficulty in deciding whether it was a 4 or a 5, though we could be quite certain it was one of the two. And so, in mongolism, though we usually assume the extra chromosome is a 21, it is still by no means certain it is not a 22.

The *6–12 group* in the middle is the biggest and most difficult to deal with. It consists of middle-sized chromosomes with the centromere neither very near the middle nor very near the end. It includes seven pairs of autosomes (which by the way means simply pairs that are always alike, as distinct from heterosomes, where the pairs are often unlike; but since in nearly all creation it is only the sex chromosomes that make unlike pairs, it has come about that autosomes in practice mean non-sex-chromosomes) and one or two X's—and so the number in the group is normally 15 in men and 16 in women. It is well defined by the distinctive wishbones 13–15 below and the almost equally distinctive pincers 4–5 above, and so it is fairly easy to count how many there are in the group (and so incidentally to obtain an independent check on sex). It is very much harder to separate the pairs within the group. Obviously one can tell one end of the group from the other: one will not mistake a 6 or a 7 for an 11 or a 12. How far one can go beyond this is a matter of dispute into which there is not much point in entering here.

It is not even certain which is the X, though it is generally supposed to be the second largest, coming between pairs 6 and 7. It is nearly always, however, possible to find an independent check of the number of X's present by nuclear sexing. With a very few exceptions (interesting in themselves, but not such as to destroy the rule) where nuclear sexing indicates one or more extra X's, the corresponding number of extra chromosomes are found in the 6–12 group, and it is always reasonable therefore to assume that this excess is due to X's.

These doubts as to the defensibility of exact identification of the whole chromosome set must not be thought to interfere at all with the reliability of the findings in the vast majority of published cases. There have been one or two mistakes, but not such as to cause damage. It does not really matter whether the mongol chromosome is a 21 or a 22: it must be one or the other, and when circumstances arise that make it necessary to decide which it is, the circumstances themselves will probably contain the seeds of the solution.

TECHNIQUE

This is no place to describe methods in detail. Perhaps what the general reader most needs to know is that they are increasingly reliable but still not easy. It is probably less difficult to analyse a well-prepared mitosis than to prepare one well. Probably it should not be attempted by any group unless at least one well-qualified person is prepared to devote full time to it.

There are three chief sources of the mitoses needed for study. All depend on tissue-culture techniques, but the length of cultivation varies widely. Classical tissue-culture methods, aiming at the production of a single layer of cells growing rapidly on a flat glass surface, can give very beautiful results; but they are costly in time, labour, and skill. The first relatively simple technique depended on the ability of marrow cells to continue dividing when kept in suspension in tissue-culture media for twelve hours or so. The most recent method uses the white cells of the blood, and depends on a curious property of phyto-agglutinin extracted from French beans. If one precipitates the red cells from a blood sample with this material and then incubates the white cells in the remaining plasma (plus synthetic tissue-culture medium) an unexplained burst of mitoses occurs about the third day. This method not only avoids sternal puncture but gives better results, and is almost universally used at present.

In the later stages of all methods colchicine is an almost invariable ingredient. It stops mitoses in mid-career, so that they accumulate and are easier to find. Also, by breaking up the spindle, it allows the chromosomes to separate, instead of lying bunched together in the familiar star-shaped mass. This spreading process is helped by making the cells swell (just before fixation) with hypotonic solutions, and by flattening them out on the slide either by judicious squashing or by air drying. There is a good deal of green fingers involved in all these processes.

Prospects

He would be a brave man who would attempt to predict the lines of future development. It may be that the present breakthrough is already near the limit of our progress for a long time—that technique will improve in simplicity and reliability, but not very much in resolving power, so that even the ability to distinguish all the chromosome pairs with certainty will still elude us. We need either bigger chromosomes or higher magnifications. For the latter ultraviolet photography might help a little, but electron microscopy will have to travel a long way before it can give useful results. Bigger chromosomes would be best of all, but we know of no way of producing them.

The tantalising thing is that a relatively small increase in resolution might yield tremendous dividends. Naturally occurring enlarged chromosomes (the giant chromosomes of the salivary glands of dipteran larvæ, or the lamp-brush chromosomes of frog eggs) show an enormous amount of detail which enables one not only to identify the individual chromosome but also to localise events along its length with great exactitude. It is nearly certain that human chromosomes, if only we could see them clearly enough, possess intensely varied individual patterns. If only we could grow them a few times their present size, or magnify them a few more diameters, we should begin to see these patterns. There seems to be no immediate prospect of either being achieved; but in this subject pessimists are continually being confounded.

Examination of meioses would of course help, at least with the pairing-off problem. But there is no known way of producing meioses artificially. Ovarian meiosis is hardly ever accessible in man; and, though testicular biopsy is a simple enough procedure, a very large proportion of the most interesting cases have disorders of spermatogenesis which make it useless. Even given a good active testicular biopsy, the technical problems of obtaining from it a preparation comparable to modern mitotic cultures have not yet been overcome.

Applications of the Method

DETECTABLE CHROMOSOME ABNORMALITIES

From what I have said so far it should be clear that any change in the chromosomes has to be gross to be visible at all with present methods. We can count the total number of chromosomes accurately, and if the number is wrong we may be able to say which is missing or in excess. If there is a structural abnormality of a chromosome we may be able to recognise it, but only if it is relatively massive. We may be able to recognise a loss of half a micron from a chromosome 22, because this is nearly half its long arm, but a much larger loss from a chromosome 1 will pass without notice. And the amount of genetic material in half a micron of a chromosome must be colossal. (The number of distinguishable loci in the average chromosome appears to be of the order of 100,000.)

Dismiss from your mind every idea that the genetic lesion of traditional Mendel-inherited disorders like hæmophilia or phenylketonuria could possibly be demonstrated by the kind of method we are discussing. These depend on a disorder of the deoxyribonucleic acid chain—perhaps the misplacement of a single base in the chain, one dash written for a dot in an enormously long Morse code message. It is like hoping to detect a single false note in a recording of a symphony speeded up so fast that we hear the whole in a second. The most we can manage at present is to identify the symphony from its length and the position of its main interval. Even if a whole movement were substituted by one from another symphony, we should only be able to recognise the fault if it was one of very different length from the original.

Possible Anomalies

When we consider the amount of genetic material concerned in even the smallest visible chromosome lesions, it is astonishing that any of them can be compatible with life. The answer to this is that, of the great variety of lesions, only a very small number are seen in practice. One is concerned here, of course, only with lesions that affect the whole body: what is compatible with survival of a part of the body—and especially of a tumour—is a very different matter. Tumours especially are capable of huge chromosome variations: but they do not have to achieve viability on their own account.

Loss, for instance, of one whole chromosome (*monosomy*, because only one of a pair remains) is nearly always fatal, and so is loss of a substantial fraction of one chromosome. Gain of an extra chromosome is not so bad, though still bad: every variety of *trisomy* (i.e., the presence of three chromosomes of a kind instead of the normal pair) is damaging, but several varieties at least are compatible with life and one even with reproduction.

Loss or gain of the sex chromosomes seems to be especially well tolerated. Both contain relatively little genetic material for their size, and, since there is a normal variation in the number of each kind, there must be a tolerance to such variations which is not called for with the autosomes. (To take one simple example of the way this can work, any autosome may carry lethal recessives which are bound to be exposed in the monosomic condition: but, since both are single in the male, the Y cannot and the X is most unlikely to carry any such lethal factors.) Whatever the reason, it is a fact that sex-chromosome monosomy (a single X or XO) is the only form of monosomy yet recognised, and all or nearly all the cases with more than one extra chromosome have involved the sex chromosomes.

CLINICAL MANIFESTATIONS

Between lesions that are too big for survival and lesions that are too small to be recognised, the ground is narrow. There are four well-established and reasonably common syndromes, and a great number of rarer variants, less well studied. Of the four main syndromes, three involve sex chromosomes, one an autosome; three are trisomies with 47 chromosomes, one a monosomy with 45; three are old syndromes revived, one is wholly new. Any one of these four is a study in itself: what follows is the barest bones.

(*a*) Trisomy–21 (*mongolism*).—No description is needed of this familiar, common (1 in 600 births) and precisely defined form of congenital mental defect. Its cause is now demonstrably the presence of an extra chromosome 21. As to *how* the anomaly produces mongolism we are literally clueless, but the fact is there. (Mental defect—and sterility—seem especially common consequences of chromosome anomalies, but neither is constant: XO interferes little with intelligence and XXX is often fertile.) A very few mongols have the normal 46 chromosomes, but these are the " translocation " cases (see below) in which the bulk of the extra 21 is still present but attached to another chromosome.

(*b*) Trisomy–X (the *XXX syndrome*).—These cases are women, often mentally defective, but otherwise unremarkable. They are often fertile, producing normal offspring. Probably they account for something under 1% of female mental defectives and something under 0·1% of all female births. This is the latest of the four syndromes to be described, and the only one that is not an easy clinical spot diagnosis. It carries its hallmark, however, in the buccal smear, where the duplicated sex-chromatin bodies in the nuclei are very characteristic. Cases with four or more X chromosomes occur, but much more rarely: the abnormality is probably always greater than with simple XXX. With each extra X the number of sex-chromatin bodies increases in step, the total being just one less than the number of X chromosomes in each case.

(*c*) Trisomy–XY (*XXY Klinefelter's syndrome*).—These cases, in most respects normal males, have small testicles (tubular atrophy and Leydig-cell hyperplasia) and

infertility as their only constant features. Eunuchoidism, gynæcomastia, and mental defect also feature prominently in any series. After puberty clinical diagnosis is not difficult, bilateral small soft testes without other obvious cause being always very suggestive of it. The presence of sex chromatin in the buccal smear will clinch the diagnosis. Anatomically normal male external genitalia and a chromatin-positive buccal smear are practically diagnostic of XXY. (Note that some cases of Klinefelter's syndrome are not due to chromosomal anomaly, but these are chromatin-negative.) Something over 0·2% of all male births, over 1% of male mental defectives, and over 3% of men with organic infertility are XXY. Again there are rarer and more severely affected variants with a larger number of X's, some also probably with additional Y's, and mosaic mixtures.

(*d*) Monosomy–X (*XO Turner's syndrome*).—This is the most complex disorder and fairly certainly the least common of the four. The classical syndrome is well known and well defined: a dwarf woman, with absent or grossly hypoplastic gonads and the endocrine consequences of this, and with in addition a variety of more or less constant associated stigmata—webbed neck, irregular ears and hairline, cubitus valgus, shield shaped chest with wide-spaced nipples, peripheral œdema in infancy, cardio-vascular defects including coarctation, and others. Fertility is very rare but intelligence little if at all affected.

Besides the straight syndrome there are many marginal varieties. Incomplete XO's are probably as common as the complete form: either only part of the second X is missing or, more often, the patient is a mosaic, with an admixture of XX or XY or XXX cells. In addition there is a confusing group of cases too diverse to discuss here, with some part of the clinical syndrome but no chromosomal anomaly.

Clinical diagnosis of Turner's syndrome is usually easy, at least after puberty. A buccal smear is of obvious value: the XO cases are chromatin-negative (though an exception to this is claimed) and the mosaics give intermediate patterns which may, however, need some experience to interpret. A surprisingly large proportion of cases of primary amenorrhœa are due to chromosomal anomalies, and such cases should always have at least a buccal smear (which will uncover also cases of testicular feminisation, though this is not due to a chromosomal anomaly).

(*e*) *Other abnormalities*.—These begin to be numerous, and cannot be dealt with adequately here. Trisomies have been claimed for quite a few chromosome pairs, and some (especially one in the 13–15 group, and one in the 17–18) are well established. The cases are all mentally defective children with multiple congenital defects, and the numbers of cases are too few for the certain definition of syndromes, though it is most probable that syndromes corresponding to each viable trisomy will be established in time. Multiple trisomies (especially the mongol-Klinefelter combination, 3×21+XXY) occur. Translocations, deletions, and perhaps other chromosome lesions are also involved, and may be even harder to relate to clinical syndromes. Mosaics also must be included, though those recognised so far have all been related to the four main syndromes. One triploid child, with trisomy of all pairs and 69 chromosomes in all, is the most extreme anomaly yet recorded.

Origin of the Anomalies

Almost certainly, the usual cause of the commoner and the grosser chromosomal anomalies is the process of *non-disjunction*. During the preparation for reduction division during meiosis, the two chromosomes of each pair come briefly together (the only time when they are paired off naturally) before they separate to go one to each daughter cell (haploid, with twenty-three chromosomes). If this process goes wrong, either by failure of pairing-off or by failure of separation of the pair once formed, both members of one pair may find themselves in one gamete. For example, if we consider the presumed origin of mongolism by non-disjunction in the mother (fig. 5) it is easy to see how faulty division of the oocyte can result in a cell with two 21's and another with none at all. Each normal male spermatozoon brings its single 21, and when it fertilises an ovum with two 21's, the result is a zygote with three, which results in a mongol. If it fertilises an ovum with no 21's, the final zygote has only one, and this must die at some early stage of pregnancy.

Most simple trisomies can be explained in this way. Non-disjunction increases with the age of the mother: hence the clear evidence of a maternal-age effect, at least in mongolism and the XXX syndrome. The above account disregards the existence of a second meiotic division which, however, usually results in duplication of the products of the first, so that four cells (two with two 21's, and two with no 21's, in the example given) are produced instead of two: all four survive as gametes in the male, but three are lost as polar bodies in the female. Cases with moré than three X's suggest that in the case of that chromosome at least the non-disjunction can be repeated in the second division, so that in the extreme case the four nuclei resulting would be XXXX, O, O, and O.

Though the term non-disjunction should, properly speaking, only be applied to the meiotic defect, something very similar can also occur in mitosis, both daughter chromosomes derived from one chromosome passing into one of the daughter cells. It appears that this can sometimes happen at a very early stage. For instance, at least

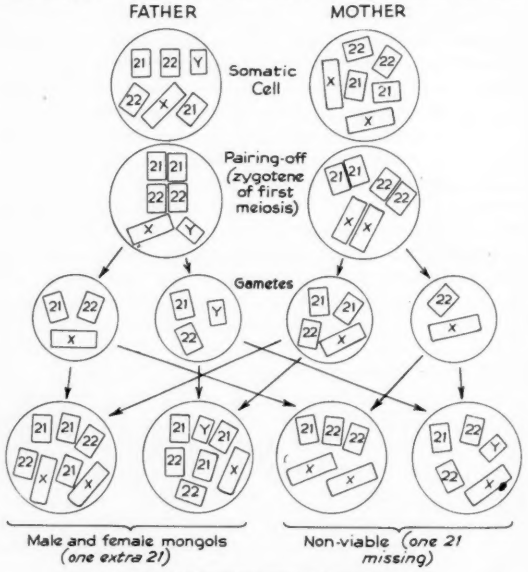


Fig. 5—Non-disjunction producing mongolism.

Most of the chromosomes have been omitted, leaving only the sex chromosomes and pair 22 (which behave normally) and pair 21 which behaves normally in the father and undergoes non-disjunction in the mother. Both 21's pass into one ovum, so that after fertilisation the offspring have three 21's and are mongols. The ovum without a 21 cannot produce a live child. (Second meiosis and polar bodies have been disregarded.)

two women are known whose bodies consist of mosaics of roughly equal numbers of XO and XXX cells. One can only suppose that such a woman began as a normal XX zygote, but that at its first division " non-disjunction " occurred with one of the X's, both of whose daughter chromosomes passed into one daughter cell, and thus of the two cells produced one had an X too many and the other an X too few. Not all mosaics arise in this way: thus, for instance, an XXY/XY mosaic may arise by early loss of an X from what was originally an XXY ovum—a remarkable example, if this is true, of accidental reversion to normal.

Translocation is so far much less important, though translocations too small to see may be common. A translocation is an exchange of material between two chromosomes of different pairs (exchange with the other member of the same pair is a normal part of meiosis). Simple exchange between two chromosomes has little immediate effect (all the genetic material is still there) though there may be defects arising from imperfections at the new joints. Since, however, the chromosomes affected are now different (sometimes very widely different) from their original partners, they cannot pair off properly during meiosis, and irregularities may arise in the offspring in consequence. Thus in some families a translocation may exist which has the effect of attaching the bulk of one 21 to another larger chromosome: in itself the translocation does not matter, and it may be carried through several generations, but it so affects meiosis that occasional members of the family acquire an extra dose of 21 and so appear as mongols, thus giving rise to the most important variety (even if rare) of familial mongolism. This is the only chromosomal anomaly yet recognised as transmissible: all the other anomalies so far known stop at the one case in which they appear.

There are other kinds of chromosomal lesion, of which deletion (loss of part of a chromosome) is the simplest, and this has occasionally been blamed for disease in man.

Acquired Chromosome Anomalies

All the diseases so far discussed are congenital, demanding a lesion already present in the fertilised ovum or (for mosaics) its immediate successors. The new techniques have so far only increased our knowledge of acquired lesions in two ways. In the first place, it has been shown that in most cases of chronic myeloid leukæmia there is a deletion of part of one of the smallest autosomes—a 21 or a 22. And in the second, it has been shown that a single dose of 250 rad of deep X rays to the spine, or 100 mC of radioiodine, produces a shortlived but surprisingly abundant crop of chromosomal anomalies. These are both profoundly interesting observations which cannot be discussed further here.

In an attempt to set down the essential facts intelligibly in the least possible space I have left out all the history, all the people, and all the original references. There are too many of the latter to give them all and to choose would be invidious. If I have failed to give credit where it is abundantly due, I apologise, but I have at least been consistent. Fortunately, so large a fraction of the formative papers in the subject have appeared in *The Lancet* that the earnest inquirer is recommended to begin with the issue of April 4, 1959, and work steadily through all the issues from then until now, using the index as far as it is available. Nearly all the people who matter are represented. You will find it heavy going in places, but most of it makes good sense, and it is a wonderful story.

Weaker vessels may find the editorials of April 4, 1959 (p. 715), Sept. 26, 1959 (p. 448), May 4, 1960 (p. 1118), July 23, 1960 (p. 191), Nov. 12, 1960 (p. 1068), and Feb. 25, 1961 (p. 433), especially the first and the last three, a better historical introduction than this, and a useful source of all but the most recent references.

The mitosis was prepared by Miss Elizabeth Boyd, the photograph by Mr. G. Kerr, and the diagrams by Mr. R. Callander.

Occasional Book

PUBLISHED OUT OF ORDER

Father Teilhard de Chardin's *The Phenomenon of Man* [1] was a sensation of the 1959–60 winter reading season, receiving tremendous notice everywhere and bearing that accolade of the lending section, *This book cannot be renewed.* Exactly a year later *Le Milieu Divin* [2] has appeared, with the following distinctions from its predecessor: its title is apparently untranslatable to English, and it has received nothing like the same acclaim. But it is essential reading for a full understanding of the first volume. For a remarkable feature of these two books has been the editorial decision to release *The Phenomenon of Man* before *Le Milieu Divin*, admitting at the same time what I think most readers would have spotted, that the latter was written before the former.

It is a tribute to publisher's clairvoyance that the huge success came first; but in all fairness the second makes the first better, while it would not have made a striking introduction to the series if it had appeared in its natural order. In *Le Milieu Divin* Father Teilhard's Christian ethic is clear and convincing, and he supplies exactly what *The Phenomenon of Man* failed to possess. There was an utter lack of divinity in that book, either revealed, available, or accessible, but *Le Milieu Divin* is a thesis on the process of " divinisation ", of both our active and our sensory lives, and is deeply moving.

Father Teilhard therefore, or rather his literary executors, have produced two books, at once mutually incompatible and mutually complementary, which is not surprising because reconciliation is Father Teilhard's specialty. Thus he is able on one occasion to stand outside his Christian faith and observe the fallacy of the Christian's resignation, going so far as to admit that the pagan loves the earth in order to enjoy it, the Christian in order to make it purer and to draw from it the strength to escape. The Christian for him is to be at the same time both the most detached and most attached person, a disparity which he varies between segregation and aggregation (strongly hinting at what is to come in *The Phenomenon of Man*), and between development and renunciation. This is agile reconciliation in all conscience, and he goes further with " spirituality of matter ", arguing platonically, if not pantheistically.

There should be more volumes to come to the English reader of Father Teilhard, but already we are very grateful for the pair which have arrived. Once their order is sorted they show the direction of his Christian adaptation to scientism. Father Teilhard was a pioneer of that frontier, as this literary testament is showing, and he seems to be winning more credit from his fellow cloth than from laboratory jackets. What criticism there was for *The Phenomenon of Man* came from biologists, and this is inevitable on the premise that a scientist must be dualist towards spirit and fact, while a priest can be universalist, and this is Father Teilhard's very advantageous position. He is dealing genuinely in Christian comfort, which is good European coin, and his editor is paying it out cunningly.

G. O. J.

1. See *Lancet*, 1960, ii, 430.
2. Le Milieu Divin. By PIERRE TEILHARD DE CHARDIN. Edited by B. WALL. London: Collins. 1960. Pp. 153. 18s.

Conferences

PSYCHIATRY, THE LAW, AND THE PUBLIC

FROM A CORRESPONDENT

A SEMINAR under the auspices of the Royal Medico-Psychological Association was organised in Gloucester and held there on May 2.

Dr. PATRICK G. MCGRATH, superintendent of Broadmoor Hospital, noted that the recent working-party report [1] had not improved on the definition of patients to be transferred to the special hospitals: they were evidently still to be persons of "dangerous, violent or criminal propensities". Of the last 100 men admitted to Broadmoor, about half were detained during "Her Majesty's pleasure" having been found insane at or before trial, and half were "time" men transferred from prisons because of intercurrent illness. Schizophrenia (the largest group) formed half of each category but affective disorders (all depressive homicides) were more numerous among "pleasure" cases and psychopaths among "time" men. It was arguable where depressive homicides should be treated, for they were not impulsively criminal nor dangerous to persons other than their nearest and dearest. In an ordinary hospital, however, they would be "isolates" and objects of much curiosity or tactless sympathy; but not so in a special hospital. Schizophrenic violence, however, varied enormously in origin and each patient needed individual assessment.

As a prison medical officer, Dr. M. A. B. FENTON said that it took 3 weeks to gather reports and fully assess a prisoner; and courts sometimes expected psychiatric reports within an unreasonably short time. This could harm the interests of the man and the doctor's reputation, but bias, if it existed, was as often towards the defence as the prosecution, and judges commonly asked specially for the prison medical officer to give a report—it seemed sometimes that defence psychiatrists laid themselves open to the interpretation that they said what the defence paid them to. As expert witnesses, psychiatrists tended to be "too medical", to report at too great a length, and to be too easily led astray by a clever prisoner. They should not be drawn into argument with a provocative advocate: to lose temper was to lose face.

Dr. G. F. BRAMLEY, as a medical officer of health, wanted to go ahead with a programme of *preventive* psychiatry but was blocked by ignorance of causes. Moving logically to *early ascertainment* as a form of prophylaxis, he said the problem was one of terminology and of the uncertain concept of the psychiatrically "normal". But these difficulties did not deter him and he wondered whether we might not come to the right techniques even in the absence of precise knowledge—as Snow had with the Broad Street pump. As psychiatrists were so few and the need so great, he counselled them not to spread themselves too far and take on too much—better let the patient travel than waste consultant time. He had doubts about whole-time local-authority psychiatrists and was glad to employ and second mental-welfare officers to work under the direction of the regional-board psychiatrist; but he wanted adequate confidential reports on discharged patients so that effective follow-up could be applied, as with tuberculous and venereal patients (a view which Dr. GEORGE B. MATTHEWS, a general practitioner, strongly condemned as running counter to medical ethics and secrecy, and undermining the position of the G.P.). But Dr. Bramley's biggest difficulty, perhaps, was in overcoming local prejudice and finding sites for local-authority hostels and half-way houses. It surprised him that informal admission since the Mental Health Act had dropped from 95% to 80% in his county, and he had doubts whether special "clubs" of diabetics, sclerotics, or psychiatric patients were really worth the cost of running and transport.

Psychiatry presented conflicting interests of law and public safety versus individual and civil liberties and, as Mr. KENNETH ROBINSON pointed out, the Mental Health Act pushed the balance further towards individual liberty than ever before. Public opinion had been more favourable than expected, and so had the Press, though they had wanted it both ways. The Press was severe about cases allegedly detained wrongfully, yet emphatic that all potentially dangerous people be kept under lock and key. The Act created new opportunities and new headaches—for example, the need for liaison or even integration between local authority and regional hospital board; and above all the care of the *psychopath*, which had been firmly laid on the medical plate. Though psychiatry must evolve new methods and there was great need for research, Mr. Robinson believed that penologists and criminologists knew even less. The public attitude of the future depended on how doctors measured up to the problem. The Minister's recent statement on the limited life of mental hospitals had been couched in brutal terms with deliberate intent to shock people out of complacency. The new units in general hospitals must be well equipped and large enough to give a comprehensive service, and must work very closely with surviving parts of mental hospitals. It was no use thinking of an acute unit as 20 or so patients tucked away in some corner and nursed in bed. Towards the public, psychiatrists should strike a balance between diffidence and arrogance, and, most important, should avoid dogmatic and doctrinaire bickering.

Lady WOOTTON viewed psychiatrists as an esoteric community speaking their own language and "looking in" at the community without really sharing in it. The lay public remained profoundly dualist and had difficulty in understanding present psychiatric incursions into the fields of law and morality. The 1957 Homicide Act recognised this invasion and the Mental Health Act did so even more strikingly. The Ingleby recommendation to raise the age of criminal responsibility was a further step. Full and logical use of the provisions for psychopathic personality could mean that in 20 years' time only first and sexual offenders among under-21s would still be handled by the courts, the rest being treated under the N.H.S. But the law still tried to draw undrawable lines between penology and medicine with harmful and absurd consequences—for example, homicides boasted *bad* records to make a plea of diminished responsibility more likely to succeed. The more wicked, thus, get the best treatment and punishment in prison was not for a man's sins but for the limitations of medical science. Future boundaries should be drawn in terms of "what works"—of what will cure and prevent the spread of infection—subject to moral limitations very much open to argument.

The willingness of the profession to extend its boundaries meant that it must be willing to treat those falling within them; and Lady Wootton criticised hospitals which refused to admit cases referred to them, or which quickly referred difficult ones elsewhere. Regarding psychiatric reports to court, of which she had read some thousands, Lady Wootton was always irritated by the mention of physical characteristics which she could well see for herself—nor did she appreciate a potted version of the facts already recorded by the probation officer.

Divergencies of opinion between psychiatrists in court came in for frequent comment (but Lady Wootton, for one, realised that these were often produced by unsound law). It is the sensational nature of these trials, and the compulsion by the defence to find a psychiatrist, somehow, who may be sympathetic, that puts psychiatric dispute into banner headlines while many other crucial differences between experts (between chest physicians on emphysema or X-ray appearances, for example) go untested in the courts and unnoticed by the public. It is sad that the psychiatrist who is only doing his best in a difficult situation should be made to suffer for the defects of an archaic legal system.

1. See *Lancet*, April 22, 1961, p. 868.

In England Now

A Running Commentary by Peripatetic Correspondents

Is your doctor out of date? The other week several newspapers came out in their frank outspoken way with articles on this subject. How, they asked, can the overworked doctor, on the verge of physical and mental collapse, possibly keep abreast of all the new trends?

"Between midnight and dawn," one of them suggested, "he awaits the peremptory ring of the emergency call from a patient." For myself, I sleep awaiting nothing; and, if the phone does ring, I am incredulous that anybody should not be able to wait until morning. A farmer once woke me out of a deep sleep to ask me to leave out some tablets for his wife. It was quite dark outside. "Surely you could have waited until the morning, and not wakened me up in the middle of the night," I said testily. "But doctor," the farmer said, "it has gone half-past six."

Another suggestion was that the poor doctor "has hardly even time to sign the death certificate before rushing to the next patient". On those rare occasions when I have a death certificate to sign, I get up early and make sure that I am not rushing anywhere. I sit back and rough it out in my mind, step by step, letting my imagination have full rein. Then, cause and effect in due sequence, with quiet conviction—for who can say I am wrong?—I slowly and clearly write it all down. For the interval between onset and death I put down, say, eight years with all the sureness of one who was crawling down the coronary arteries, torch in hand, and witnessed the very first atheromatous deposit.

Still, it's nice to think that the Press realise that the doctor *has* difficulties—even though they haven't hit on the ones that worry him most.

* * *

When I reach Euston I usually walk, for early on a clear crisp morning London is delightful. I always feel the sweet and sour of nostalgia as I turn into Gower Street. The bearded and beatnik students of today are no different from my contemporaries. I turn right between the Medical School and University College Hospital. For a moment I am disconcerted that the white-coated house-officers hurrying across from breakfast to the casualty department do not recognise me—but why should they—it was twenty years ago and they are as much occupied with their work as we were in those days of blackout, air-raids, and incidents. And then into Tottenham Court Road. Here I am, as one from Tibet or from Outer Space, and I feel apart and detached as I look around me at Londoners hurrying to work.

None of them sailed last night from the Western Isles with the azalea-red suffusion of the great cloud-banks over the gun-metal grey of the deep ancient ice-sheared loch. None travelled, as I did, on the single-line railway through the darkening hills with the flickering light on the croft up on the shoulder. None woke in the night at Carlisle or were called with tea at Bletchley and given (oh civilised joy) the morning *Times*, or shaved as we rushed down the dip slope of the chalk from Tring past the Ovaltine Farm to the Reading bedcuttings south of Watford. And none of them will return, as I will, to the celtic fringe, to the islands where civilisation is old, to the people who conceive of today as another yesterday, to the edge of the cliff that looks West where we can feel as small and as lonely in space as any astronaut. Yes, after 8.30 A.M. London does seem crowded.

* * *

Theatre Sister has been having some alterations done to her flat, which originally formed part of a mid-Victorian house; and in the consequent upheaval a copy of the *Morning Star*, dated March 11, 1867, has come to light. It carries a long letter from a reader urging support for a private Member's motion proposing the abolition of capital punishment. He wrote:

"I have thought that it would be useful and timely to adduce here a few very recent facts illustrating the utter confusion and other evils which even under the best administration of the law are inseparable from the capital penalty."

Among the cases he cited was that of a youth named Francis Bradley who "had been brought up without a home or a friend" and was hanged at the age of eighteen though "Victor Hugo with many others interceded for him". The *Morning Star* reader went on to point out that executions tended to produce other murders by morbid imitation and

"Immediately after specially notorious hangings such as those of Muller and Dr. Pritchard recently, there were sudden crops of murders or attempted murders, ten or a dozen in each case, within 3 or 4 weeks".

Moreover, he believed that capital punishment evoked sympathy for the executed criminal rather than for the victim, and many countries had successfully abolished the death penalty, always with increased security to life.

"Thus for nearly a hundred years abolition has been carried out in Tuscany and in Russia (as to murder), in Portugal and several of the United States for 20 years, in Switzerland for 30 years and in other States for shorter periods."

It all sounds very familiar, and it is hard to believe that it was written nearly a hundred years ago.

* * *

Pep pills are in the news again and they do make us think. There was the bride-to-be who swore she couldn't last out the ceremony. A tablet an hour before it was her answer to a maiden's prayer. There was the schoolchild who swore she'd fail in every subject in her G.C.E. A tablet gobbled up with her bacon and egg at breakfast during exam week helped her to confound her friends and gain nine passes. For good or ill pep pills have come to stay, and for emergencies and the occasional depressive they certainly live up to their name. But what is wrong with the common-or-garden glucose tablet? They are effective in stopping a screaming child, they sustain a tired midwife at midnight, they give the busy primip. just the extra incentive to work even harder. At 2 A.M. when resistance is low and the phone rings they can take us out to the acute abdomen, the coronary, or the threatened mis., perhaps not with the joy of living of our first cases in general practice, but without that sinking feeling which night calls in the early hours used to bring. And we can lose them by the hundreds in the street and the police couldn't care less.

* * *

"The danger o'er, both are alike requited,
God is forgotten, and the Doctor slighted."

But not by Rachmaninoff, who dedicated his now famous second piano concerto to Dr. Dahl. I had always felt that the second movement, with its obsessive harking back to the compellingly insistent main theme for the piano, was like a man groping his way through a swamp; he clings, as it were, to such small footholds as can be discerned. Now that I know its history, I realise that it gives a classical portrayal of a depressive state.

Here are Rachmaninoff's own words: "A paralysing apathy possessed me. I did nothing at all and found no pleasure in anything. Half my days were spent lying on a couch and sighing over my ruined life."[1] He was in that condition, so fatal to the creative artist, where his taste was at war with his inspiration; the music of the latter being continuously rejected by the former. He was referred to Dahl, a forerunner of Coué, who achieved a cure by the process of repeating "You will begin to write your concerto . . . You will work with great facility . . . The concerto will be of excellent quality . . ." until his patient took his advice. It is interesting that it was the second movement that was first composed. As to the last movement, the river-like motion and triumphant ending seem to say "Look! I have come through!" Dahl undoubtedly deserved his commemoration, and Rachmaninoff showed courage in thus publicly acknowledging his debt.

I see that, in the B.B.C.'s *Your Hundred Best Tunes*, this concerto is listed number forty. It is more popular, even, than Beethoven's *Emperor*. Does its appeal reflect our present ills?

* * *

A nudge in the night.—"Hey, move over! You've got half the bed."

1. Rachmaninoff's Recollections told to Oskar von Riesemann. London, 1934.

Letters to the Editor

SHORTAGE OF HOSPITAL STAFF

SIR,—In Leicestershire 183 hospital beds have had to be closed because of the shortage of nurses.[1] At the West Middlesex Hospital 160 beds are closed for the same reason. These are not isolated instances. Inquiry reveals that, although there are more nurses in the country than ever before, there is a widespread shortage in hospitals. This shortage constitutes a serious threat to the hospital service, yet the Ministry, although they must know of it, appear unconcerned.

Young women are in demand: they storm the universities, and are competed for by schools, hospitals, industry, offices, shops, and young men. Incidentally the teaching hospitals with a continuous supply of eligible young men—tethered prey—have virtually no nursing shortage. If the service in the large non-teaching hospitals is to be efficiently maintained—and about 90% of the hospital work of the country is carried out in them—something will have to be done.

First, we must know the facts. How severe is the shortage, and how is it distributed? How many beds have had to be closed in the past 6 months because of it? The Ministry must know the answers. As the problem is almost certainly national, many of the remedies that suggest themselves will be nationally applicable.

Are nurses paid enough? Clearly not, by the test of the market. Now that the nurses' working week is shorter why cannot they be paid overtime rates? Are the Ministry seriously considering increasing the rates of pay for all the nursing grades? Have the Ministry taken up with the Treasury the urgent need for taxing married women's earnings more realistically?

If nurses prefer the relative independence provided by working in an agency cooperation, or as a district nurse or health visitor, to the regimentation in the hospital service, should the Ministry penalise the hospitals by severely restricting the employment of agency nurses—as they have done—if the alternatives are to close, or keep closed, badly needed beds?

Is this the time, when hospitals desperately need more pairs of hands, for the General Nursing Council to stiffen the educational requirements for student entry? Are the existing requirements really inadequate? Is it rational, at this juncture, to introduce the teaching of midwifery and psychiatric nursing into the 3-year general training for the S.R.N. diploma? The result will be to take student nurses away from general wards for 3–4 months at a time when they are becoming most useful, towards the end of their training.

A good deal can be done locally. Student nurses must be treated as students. They must be decently housed and fed, and their individuality must be respected. They are neither religious novices nor conscripts; and matrons, administrative staff, and doctors must recognise this. A break with the old-fashioned nurses' home is imperative. Architects may recognise this need when new accommodation is being planned for nurses, but do their clients?

What the hospitals lose in nursing labour by treating nurses as college girls (that is, as students) must be made good by recruiting more qualified nurses into hospitals. The pattern of female employment has changed. The hospitals can no longer be run on the large supply of dedicated spinsters who were available between the wars; and this fact must be realised. Nowadays a short period of employment or professional training is followed by marriage and the raising of a family, and then a proportion of women return to their old profession or take a new job. The nursing administrator in a hospital should not merely tolerate married nurses, but actively welcome them in spite of the extra trouble involved. The argument that the whole-timer will be offended at the concessions necessarily made to the married nurse is ill-founded. Where does it come from? Seldom from the student nurse. It is a mistake to underrate the intelligence or the idealism of the young; and their turn will come. Matrons should point this out.

Intelligently directed local advertising campaigns will be necessary to bring the nursing shortage home to the local population—if they do not know the facts, they cannot respond.

We shall have to increase our recruitment of nurses from abroad if the local supply is inadequate, but this, although it means more trouble for matrons, should benefit both this country and the Commonwealth. Trained nurses are in great demand everywhere.

Men should be encouraged to take up nursing and they must be given the prospect of a reasonable career. They would not leave after training as so many women do. So far only the mental hospitals have provided satisfying careers for male nurses.

No amount of exhortation will attract the number of women we need into nursing unless the pay is improved, and unless rigid attitudes about discipline, residential requirements, and hours of work (for part-timers) are abandoned.

It will be difficult for the Ministry, hospital management committees, nursing hierarchies, and hospital medical staff to accept and actively to implement all these proposals. But the Cohen minority report is over 10 years old now and its ideas are no longer new. And what are the alternatives?

E. A. DEVENISH
N. F. COGHILL.

West Middlesex Hospital, Isleworth.

1. *Times*, Feb. 24, 1961, p. 7.

RESULTS OF LEUCOTOMY

SIR,—In the summary of the recent Ministry of Health report, Leucotomy in England and Wales (discussed in your annotation of April 29), it is stated: "By amalgamating the grading scales for those in hospital and those discharged, including estimates for not followed-up cases, it was found that 36% of men and 44% of women were said to have been at least greatly improved after operation. . . ." These conclusions have been widely reported, but I feel that the authors have not provided sufficient evidence to prove their validity.

Firstly, we are told that 462 patients who had two operations were excluded from the survey. This is more than 4% of the total, and one cannot help wondering how these patients would have affected the results if they had been included.

Secondly, if we look at what is meant by "at least greatly improved" we find that it means in many cases "improvement not amounting to social recovery, but sufficient to enable patient to live outside hospital so long as financial support and some supervision is provided". As I see it, this may mean a great deal or nothing at all, according to the condition of the patient before the operation, and this we are not told. But we are told that ". . . the information that hospitals could reasonably be expected to supply would be limited to facts and observations that would normally be recorded in the case notes of the patients concerned". I should like to be sure that this question in the survey was answered not only in regard to the final condition of the patient as recorded in the notes at the time of discharge, but that it was also related to his original state.

Finally, I should like to question the validity of a most important assumption. This is that "is seems reasonable to assume that the group of discharged patients who had kept in touch with the hospital and were thus available for clinical grading had, on the whole, responded less favourably to leucotomy than those who did not seek further attention". That this is important we see when we read that 3068 cases out of 4768 discharged were not followed-up, but that the results for discharged cases were assessed as if the followed-up and the not-followed-up cases were similar. I could find no evidence in the report to support this assumption.

On the other hand, the converse could be argued as follows: that leucotomy is the final treatment available when all else

fails; that all the hopes of patient and relatives are directed towards a favourable result; that if there is no improvement there may be despair and anger and that this may be a good reason for not returning for follow-up. Of course, this is also no more than hypothesis, but nevertheless it would be interesting to know how many of the not-followed-up patients were discharged by the hospital and how many failed to keep an appointment. It would also be interesting to know how many patients were being followed-up in hospitals other than the one by which the operation was recommended or performed.

London, N.W.11. J. F. SHAW.

INDIAN CHILDHOOD CIRRHOSIS

SIR,—We were very much interested in the comments of Dr. Robinson (April 15) on our article (March 18).

Undoubtedly a number of hepatotoxic plants have been described in India, but our point is that such plants are never used by the patients. But in Jamaica extracts of such plants are used for preparing herbal medicines or in the form of a beverage—bush-tea. There are no such customs in the part of India from where we described our cases. The characteristic localisation of the disease to a particular sect of Hindus, the involvement of a number of siblings in the family, and the overwhelming preponderance of boys are all too significant to be disposed of as due to " custom rather than inheritance ". There is hardly any doubt that Indian childhood cirrhosis is a genetically determined disease.

Medical College, Patiala, India. AMARJIT SINGH S. S. JOLLY.

SCIENCE, GOVERNMENT, AND DEMOCRACY

SIR,—The fundamental problem posed in your leader of April 22 might have been headed more correctly Scientists, Government, and Democracy. What in fact you discussed was the relationship of these three aspects of society, aspects with fairly well-known characteristics. Your final lament for democracy is hardly justified by the particular starting-point of the debate or the issues raised.

Of the original debate it is enough to say that had the democratic tradition of this country been less effective the " cult of the individual " would have led to even greater concentration of power in fewer hands with results that have been noted, to some disadvantage, in other countries. Men of science are still very much men, and the central issue is to what extent, and how, political leaders should delegate authority into the hands not of " science " but scientists and professionals and how these can be directed and controlled, bearing in mind Shaw's dictum that every profession is a conspiracy against the community, and the older, no less apposite fable of the giant Antius who, when he was not in touch with mother earth, soon lost his strength.

Since scientists, Government, and democracy are not independent variables (particularly the latter two), it is often likely that Governments will choose for their committees those who represent the orthodox line (if no more), and by the fact of being on such a committee the conformists will tend to conform even more. But however technical the problem that is presented, the decisions in its resolution pass far beyond the experts so that the scientist is often thrown back on to his prejudices which are known to be no less strong than those of the non-expert. (It is after all only in a narrow sector of a very broad front that expert advice is what it claims to be.) It is therefore only by increasing the democratic cover at the apparent risk of diluting quality and increasing committees that this fundamental risk can possibly be avoided.

Leaving aside those instances where Governments set up committees with no greater object than that of marking time, excluding those instances where committees are so linked with vested interests of personal commitments (not uncommon in other parts of the world), the basic problem remains how the community through its Government can best tackle the very complex problems of politics and social organisation, using experts but avoiding possible prejudices of experts. (How attractive it is to believe that the expert is above the battle, and that we can shed our own responsibility leaving it to the leaders.)

The thermodynamics of democracy are capable of varied explanations, but there would seem to be more danger in no debate than of the debate continuing. There can be no inbuilt control which will absolve the community of keeping itself well informed and taking responsibility for final decisions. It is probably true that the more informed the debate the more seriously will the Government—and committees—attend to their business.

The problems of the N.H.S. do not spring least from the fact that there has been little attempt to shoulder the community with their responsibility and have an enlightened and informed democracy. For this the Government and possibly the committees must bear their share of responsibility, though in the final analysis you may be right in laying the bulk of the blame on the public; but this is the result not of too much but of too little democracy.

Moseley, Birmingham. B. BARNETT.

PSYCHIATRY FIFTEEN YEARS AHEAD

SIR,—Having experience both of the very large mental hospitals of the present day and of a 228-bed psychiatric unit (with a full complement of " long-stay " patients) I should like to comment on Dr. Pilkington's letter of April 15.

Since there are very few similar units in this country, for those who have experienced only the very small observation ward or mammoth mental hospital there may seem no great urgency in creating more small comprehensive units. It may be felt that the larger institution is simply a smaller one writ large, or multiplied. I feel very strongly that despite the highest standards and the most conscientious and energetic efforts, the massive mental hospital must always have an anti-therapeutic effect.

In a community of 228 patients, plus staff, such as the one I know well, the team treating the patients has a far easier task in effecting, continuing, and promoting therapy, and in maintaining regular trained oversight for all patients. Coordination and effective work with local-health-authority staff, social workers, psychologist, and so on, is very much easier and more continuous with a tightly knit team.

The discharge into the community of patients with certain residual symptoms really requires intensive and often quite frequent follow-up, for which in the present state of medical and auxiliary staffing of most mental hospitals it is almost essential that the local-authority network of staff should be brought in. This is much more readily obtained with medium-sized units, situated in the communities they serve.

The disadvantages of the mammoth mental hospital are, of course, well known, but I think underrated by most people who have not experienced a small uncluttered comprehensive unit of about the size I have mentioned. In large institutions it seems almost unavoidable that from time to time staff will be shifted around from ward to ward, often coming into contact with patients that they do not or barely know. This discontinuity of ties tends to produce insecurity in the patients and does not on the whole seem to be a good thing. In a compact unit such changes are not nearly so upsetting since the staff will know all the patients reasonably well in every section of the smaller unit they are on.

The enormous and forbidding mass of buildings and people; the labyrinthine corridors; and the many unknown faces, are the reverse of helpful to mentally ill and isolated patients; of course subdivision into small units, wards, and villas, on a more human scale, helps to mitigate this; but the large institution is always in the background.

Again, some of the most valuable staff of all departments and categories are looking after and treating other staff; instead of

patients. This appears an inevitable process with growth in size to really large proportions. In a unit of reasonable size communications to all levels are much easier.

Lastly, let us not forget why these buildings were placed where they are and built as they are. The scale and site of the buildings stand for, and must to some extent (whether we like it or not) help to perpetuate, an attitude of mind. I write because I feel that Dr. Pilkington's admirable letter, while having the positive merit of encouraging the continuing improvement of large mental hospitals, might tend to take the steam out of the really urgent need for much smaller and more human-sized units in the communities they serve.

Severalls Hospital,
Colchester. H. JACOBS.

EXTRAPULMONARY INFLUENZAL INFECTION

SIR,—I was interested to see from your annotation (March 4) that visceral invasion by the influenza virus is being increasingly recognised.

You did not refer to the 30 cases of encephalitis we reported from India.[1] These were all associated with the influenza epidemic of 1957. Several cases occurred almost simultaneously in small groups. Jaundice, presumably the result of liver involvement, was present in a third. The clinical course was characteristic. As against the negligible overall mortality in the 1957 epidemic of Asian influenza in India, the mortality in this group was very high: 17 of the 30 patients died. At necropsy, performed in all 17, typical pulmonary lesions of influenza were invariably seen. The virus was isolated from the lungs in 5 cases, and from the brain in 1.

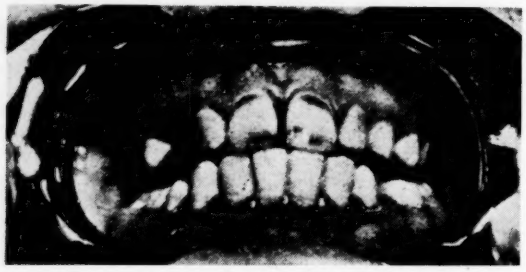
We were unable to find any reference to similar cases in the literature. Symptoms and signs of this type may not be uncommon, but may easily be missed because of pressure of work in epidemics.

Tata Main Hospital,
Jamshedpur 1, India. S. KAUL.

SKELETAL FLUOROSIS

SIR,—May I briefly reply to the letters of Dr. Patton and Mr. Fletcher (May 6)?

The data in Galagan and Lamson's paper[2] on dental fluorosis observed in temperate climates in the U.S.A. is that from Dr. H. Trendley Dean, the recognised "father" of fluoridation. It is stated that fluorosis was present in 12%, and questionable in a further 35% of the children examined in a community where the water fluoride concentration was 0·9 p.p.m. This fluorosis is described as "mild" in 2% and "very mild" in 10%. The attached photograph shows one



of Dr. Dean's admitted cases of "mild" fluorosis. It is this appearance which I had in mind when I referred in my letter (April 8) to less objectionable mottling occurring in the temperate zone. To many of us this degree of mottling is quite objectionable and as others have stated "the determination of whether damage resulting from dental fluorosis is 'objectionable' is a matter for the person whose teeth are affected and not for the arbitrary assertion of public officials".[3]

1. Kapila, C. C., Kaul, S., Kapur, S. C., Kalayanam, T. S., Banerjee, D. *Brit. med. J.* 1958, ii, 1311.
2. Galagan, D. J., Lamson, G. G. *J. publ. Hlth Rep., Wash.* 1953, **68**, 497.
3. Medical-Dental Adhoc Committee on Evaluation of Fluoridation Report. New York City, 1959.

Mr. Fletcher will observe that the reference in my letter of April 8 to the fact that 200,000 children have become victims of definite life-time mottling is quoted at the end of the pertinent paragraph, and I suggest he reads the original document in full. As Nesin wrote in 1956[4] "the number of critics capable of examining the fluoridation program on the basis of its scientific and statistical claims have increased tremendously, so today we find many importantly placed individuals seriously questioning almost every aspect of the fluoridation proposal".

Exner[5] writes of the recent legal interrogation of Dr. H. Trendley Dean: "It is because all claims of the fluoridators are based directly or indirectly on writings of Dr. Dean that his cross examination of May 13th, 1960, has such far reaching importance. It destroys once and for all, the scientific basis of fluoridation".

Institute of Pathology,
Royal Infirmary,
Cardiff. R. A. HOLMAN.

BRONCHODILATORS AND CORTICOSTEROIDS IN ASTHMA

SIR,—It is of great interest to see the considerable extension of our preliminary work[6] reported by Dr. Hume and Dr. Rhys Jones.[7] I have continued to find the method of practical value in selected cases and can confirm the correctness of the general trend of their observations.

I am sorry to see the rather free use of the word "emphysema", if only because a few patients with the clinical diagnosis of "emphysema" with a persistently severe obstructive ventilatory defect and a persistently poor response to ordinary bronchodilator drugs occasionally respond dramatically to steroids together with bronchodilator therapy. The pattern of response then conforms to that of the asthmatic patient, although normal values are never reached for $F.E.V._{1\cdot0}$, or for $F.E.V._{1\cdot0}$ expressed as a percentage of the vital capacity. This group is admittedly small, but it is striking; a lead is usually given by the presence of sputum eosinophilia. Probably these patients do have some "emphysema"; but if this term is taken to imply structural change and if the diagnosis is assumed when the bronchodilator response is poor and apparently unpredictable, then a small proportion with an obstructive defect which can be reversed only by steroids will be overlooked.

As regards the haphazard response of the $F.E.V._{1\cdot0}$ to bronchodilator drugs in structural emphysema, an observation I can confirm, it is of interest that if the vital-capacity response is plotted in the same way, a predictable curve similar to, but smaller than, that of an asthmatic is obtained. This statement is true only if the vital capacity is estimated in the conventional unhurried manner, and not if it is taken from a forced expiratory spirogram. This finding strongly supports the authors' suggestion that the haphazard response of the $F.E.V._{1\cdot0}$ in emphysema has a mechanical basis.

The evidence for the suggestion that the curve of patient B in fig. 2 represents the effect of emphysema plus reversible bronchoconstriction does not seem clear to me. My experience suggests that this patient's vital capacity would also be low (as is her $F.E.V._{1\cdot0}$), and that the $F.E.V._{1\cdot0}$ expressed as a percentage of the vital capacity would be in the normal or low-normal range rather than below 40% as is the rule in established emphysema. In other words, this curve is a typical response of a patient with a mixed obstructive and restrictive defect, and does not differ essentially from that of patient A except in the range of response. If this guess is wrong, then on what grounds is the diagnosis of emphysema based?

University Department of Medicine,
Royal Melbourne Hospital,
Victoria, Australia. BRYAN GANDEVIA.

4. Nesin, B. C. *J. Maine Water Utilities Ass.* March, 1956.
5. Exner, F. B. Fluoridation, 1960. The Greater New York Committee Opposed to Fluoridation, 342, Madison Avenue, New York, 17.
6. Hume, K. M., Gandevia, B. *Thorax*, 1957, **12**, 276.
7. Hume, K. M., Rhys Jones, E. *Lancet*, 1960 ii, 1319.

SCARLET-FEVER-LIKE ILLNESS DUE TO STAPHYLOCOCCAL INFECTION

SIR,—I was interested in the paper by Dr. Dunnet and Dr. Schallibaum.[1] Case-reports of staphylococcal sepsis with exanthem had already been published before 1910, and I recall that erythematous scarlet-fever-like exanthems were observed in *Staphylococcus aureus* and streptococcal septicæmia. The scarlet rash produced by paralysis and dilatation of the superficial vessels of skin and mucosa is also found in smallpox, german measles, prodromally in chickenpox and in measles, and in patients poisoned by food, drugs, or enemas.

Scarlet fever itself was recognised as an acute localised toxæmic infection of unknown cause. *Streptococcus hæmolyticus*, which I suggested as the cause, was found nearly always in the nose; and the organism was isolated between 1910 and 1911 in about 420 patients with scarlet fever. The cardinal symptoms were not the exanthem—sometimes present—but the enanthem, the exudate, the tonsillitis, the strawberry tongue, and, last but not least, the circumoral pallor. The picture of scarlatinal sepsis was very similar to that of *Str. hæmolyticus* sepsis in puerperal and surgical cases, but not so like that of staphylococcal sepsis. *Staph. aureus* infections—much feared nowadays for their infectivity—then differed not only in their history but in their clinical course, and differential diagnosis was not difficult, even when a scarlet-fever-like exanthem was present.

Edinburgh. R. ASCH.

NOT FOR SALE

SIR,—During 38 years of general practice I have been forced many times—certainly hundreds—in the interests of my patients, as well as of my practice, to ask a consultant to do a domiciliary visit for the main purpose of getting a non-emergency but nevertheless seriously ill patient into hospital. In no other way I found (by making many time-consuming and nearly always futile telephone calls to hospitals) could I secure the admission to hospital of such patients within a reasonable time.

The domiciliary-visit/hospital-admission racket (I don't think *we* should shrink from calling a spade a spade) is much more widespread than is generally realised because general practitioners—who play an essential role—tend to keep silent and even to deny it happens often. They must realise—though possibly dimly—that it is unfair, and the consequence is feelings of guilt (at having taken part), repression, silence, and denial. Many G.P.s, no doubt, do not wish to risk offending consultant colleagues; and the racket has been going on so long—at least 100 years, I should say—that they take part in it almost automatically.

A few years ago I sent an emergency case into hospital through the Emergency Bed Bureau. The consultant in charge of the ward he went into was cool and off-hand with him, and this contrasted sharply with his treatment of the other patients. My patient was puzzled and made inquiries, evidently, during his stay in hospital with a view to solving the mystery (of the cool consultant!) because he informed me, unasked, after he came out of hospital that every patient in the ward except himself (there were 30 beds in the male ward) had been seen by him at his home before admission. The consultant had clearly resented the admission to his ward of even an emergency case without the usual " admission fee ".

I should like to support Dr. Dunlevy's suggestion (April 29) that a committee of inquiry be set up by the Ministry of Health on the lines he indicated. In particular, the committee might inquire into the number of patients discharged from hospital from the care of particular consultants who had been seen by them in their homes before their admission, and how long they had had to wait for a bed. I also suggest that each patient be asked " what, in your opinion, was the main reason why your doctor called in a specialist to see you before you went into hospital ? ".

Wallasey, Cheshire. LENNOX JOHNSTON.

1. Dunnet, W. N., Schallibaum, E. M. *Lancet*, 1960, ii, 1227.

THE ACTION OF HEPARIN IN ISCHÆMIC HEART-DISEASE

SIR,—The role of the anticoagulant heparin in blood coagulation and its importance in the thrombotic state are problems which are still not completely understood. In their paper (April 22) Dr. McDonald and Dr. Edgill devote much attention to the theoretical aspects of these questions.

They refer to my work [1] published in 1956, which indicated that coagulability increased after thrombosis and embolism, and to their own similar findings published in the following year.[2] They also discuss possible reasons for the acceleration of clotting. They quote me as saying that resistance to heparin noted after a recent thrombotic episode is due to raised factor-VII activity. This is not quite in accordance with the views I expressed [3] in 1957, and cannot be reconciled with my recent papers on the subject.[4 5]

Possibly this is important, so it might be worth describing the evolution of ideas on the subject. Resistance to the anticoagulant action of heparin was noted in 1944 by Waugh and Ruddick [6] and later confirmed by others. In 1956, using a simplified technique, I showed that the differences in different thrombotic disorders were statistically significant.

The investigation into the thrombotic state [3] employed a battery of coagulation tests to determine the nature of " accelerated " clotting in these patients. Two significant findings emerged: (1) thromboplastin generation was increased in patients with thrombosis compared with controls; (2) increased factor-VII activity was present after thrombosis.

The first finding was presented tentatively because the differences, although significant, were small and confirmatory evidence was lacking. But in the same year McDonald and Edgill [2] reported increased thromboplastin generation in patients with ischæmic heart-disease. Several recent papers have confirmed that thromboplastin generation increases in patients with thrombosis.[7–9]

The finding of increased factor-VII activity in the thrombotic group was of great inrerest. Several authors had previously demonstrated increased factor-VII activity in pregnancy, which they had regarded as evidence of a hypercoagulable state.[10 11] My unpublished experiments had shown there was present in stored normal serum, and in extracts of serum with much factor-VII activity, an agent which neutralised the anticoagulant effect of heparin. With a completely different approach, by infusing serum extracts experimentally, Wessler [12] in the United States found that rapid thrombosis resulted from the administration of serum extracts rich in factor-VII activity. It thus appeared more likely that heparin resistance in thrombosis was due to the raised factor-VII activity.

The anti-heparin activity of serum was then studied in sera obtained from patients with different serum coagulation defects. Batches of factor-VII-deficient sera, sera from patients with severe Christmas disease, and from patients on phenindione with severe impairment of " intrinsic " thromboplastin production were compared with normal serum and saline in a heparin-plasma-clotting system. Christmas-disease

1. Poller, L. *Clin. Sci.* 1956, **15,** 55.
2. McDonald, L., Edghill, M. *Lancet*, 1957, ii, 547.
3. Poller, L. *J. clin. Path.* 1957, **10,** 348.
4. Poller, L. *ibid.* 1960, **13,** 226.
5. Poller, L. *Post Grad. med. J.* 1960, **36,** 564.
6. Waugh, T. R., Ruddick, D. W. *Canad. med. Ass. J.* 1944, **51,** 11.
7. McDonald, L., European Congress of Hæmatology, abstr. no. 194. London, 1959.
8. Spittel, J. A., Pascuzzi, C. A., Thompson, J. H., Owen, C. A. *Proc. Mayo Clin.* 1960, **35,** 37.
9. Lempert, H., Poller, L. *Lancet*, 1960, ii, 1115.
10. Koller, F., Loeliger, H., Duckert, F. *Rev. Hémat.* 1952, **7,** 156.
11. Alexander, B., Meyers, L., Goldstein, R., Gurewitch, W., Grinspoon, L. *J. clin. Invest.* 1954, **33,** 914.
12. Wessler, S. *ibid.* 1955, **34,** 647.

(factor-IX-deficient) sera had less effect than the others, but all significantly accelerated clotting. The anti-heparin agent was removed by absorption with alumina in the same way as Wessler's thrombotic agent of serum. Serum obtained from carefully collected platelet-free plasma did not differ from normal, which made the assumption that the anti-heparin action was due to anti-heparin activity of platelets unlikely. The physical properties of the serum heparin antagonist resemble those of the thrombotic agent of serum described by Wessler and Reimer.[13]

The fundamental question is whether increased coagulability assessed by heparin resistance and other tests is a cause or a by-product of thrombosis. My results suggest that the general increase in clotting activity, as opposed to the local changes in coagulability, in patients with thrombosis may be, in part at least, a secondary phenomenon due to the release into the circulation of serum products from a formed thrombus, rather than a primary hypercoagulable state.

Department of Pathology,
Withington Hospital,
Manchester. L. POLLER.

TREATMENT OF FRIGIDITY

SIR,—We have had many inquiries about the treatment of the vaginismus and frigidity in the wife of the transvestite described in our letter of March 18.

She was 28, and had been married for over four years. She was seen initially when her husband's case was being investigated. She was then completely unaware of his deviant behaviour, which had antedated their marriage by many years.

The marriage had never been consummated because she invariably had pain and spasm when intercourse was attempted. After six months' marriage she was referred for gynæcological examination; the hymen was incised, and dilators were passed. Her symptoms continued, and she was still unable to achieve intercourse. She was reluctant to discuss her sexual difficulties, and became tense and inhibited when she tried to do so, although it was clear that she fully understood the physical aspects of marriage. Even contemplating the sex act seemed to produce strong anxiety; so simple relaxation exercises were initiated and progressively deepened to the hypnotic state, starting at the first treatment session. During this period positive suggestion only about relaxation was given—e.g., "You are finding it easy to relax", "it is pleasant to relax". On this occasion no reference was made to sexual matters.

The hierarchy of anxiety-provoking stimuli was simply the hierarchy of events normally terminating in intercourse; hence we presented the sexual situation in a hierarchical fashion starting with ordinary affectionate gestures and ranging through foreplay to the initiation of coitus. Agitation exhibited (shown in earlier sessions by a tendency to emerge from the hypnotic state) was our guide to the degree of anxiety generated. Whenever this became apparent relaxation was reinforced simply by suggesting the pleasure of relaxation associated with the particular stimulus—e.g., "It is pleasant to relax", "It is pleasant to relax when you are kissing your husband" repeated over and over again.

In all she had five sessions of an hour each at weekly intervals. In the sixth week she reported successful and satisfactory intercourse; and now six months later she is in the second trimester of pregnancy.

Hypnotic techniques are recognised to produce occasional good results in vaginismus and frigidity. We submit that where these and other methods are successful it is by virtue of a common factor—the deliberate or unwitting application of learning theory.

In the course of psychiatric examination and assessment "dynamic" factors did emerge; but for purposes of treatment they were deliberately ignored. In this instance a cure was achieved by treating the symptom itself—"by extinguishing unadaptive conditioned reflexes and establishing desirable conditioned reflexes".[1]

Whittingham Hospital,
near Preston,
Lancashire. J. D. GLYNN
P. HARPER.

DICHLORPHENAMIDE IN CHRONIC RESPIRATORY FAILURE

SIR,—I read with interest the reports by Dr. McNicol and Dr. Pride (April 29), by Naimark et al.,[2] by Dr. Harris (Feb. 18), and by Dr. Wahl and Dr. McCarthy (March 18) on the usefulness of dichlorphenamide in respiratory insufficiency with hypercapnia. I should like to add my experience with 6 patients.

Their diseases were: pulmonary fibrosis 1, chronic bronchitis with emphysema 2, and cor pulmonale 3. Most patients were admitted with acute respiratory infection and the maximum possible benefit was sought by routine treatment with antibiotics and bronchodilators. When a basic steady state of health had been attained, all still had clinical evidence of respiratory insufficiency and a raised pCO_2.

Dichlorphenamide was given daily (100 to 200 mg. in two doses) for ten to fifteen days. Assessment of the effect of the drug was based upon change of effort tolerance and pCO_2 measurement by the rebreathing method described by Campbell and Howell.[3]

In 1 patient severe headache developed two days after the onset of treatment. 1 of the remaining 5 complained of mild nausea, but treatment was continued.

In 4 of them increased effort tolerance and a greater feeling of wellbeing was noted, accompanied by a fall in pCO_2, averaging 10 mm. Hg. In 1 case (cor pulmonale) though the effort tolerance was remarkably improved not much change was observed in pCO_2. But this patient and 1 other, with pulmonary fibrosis, admitted that they had never been so well in the past three to five years as they were after dichlorphenamide.

I am greatly indebted to Dr. P. G. Arblaster for kind permission to report these cases.

King Edward VII Memorial
Chest Hospital,
Hertford Hill, Warwick. M. T. AHUJA.

FŒTAL ABNORMALITY

SIR,—I was interested in Dr. Kohler's observation (April 29) that the peculiar facies described by Potter [4] was associated not only with renal agenesis, but also with other urinary-tract abnormalities, including urethral obstruction by mucosal folds and severe phimosis; and that all these cases had had oligohydramnios or anhydramnios.

Hilson [5] also reported that abnormalities of the urinary tract such as a bifid ureter or absent kidney may be associated with facial abnormalities, similar to the Potter facies, the ears in particular being affected. Browne [6] has taught for many years that compression of the fœtus by the uterine wall may cause mechanical deformities, and Davidson and Ross [7] reported 6 cases of the Potter syndrome, all of which had club foot. It seems probable, as already suggested,[8 9] that the Potter facies may also be due to compression. This compression would explain the flattening of the nose, the receding chin, and the malpositioned ears.

This suggestion is supported by observations made on mammalian fœtuses (rat and rabbit) after intrauterine surgery.[10]

13. Wessler, S., Reimer, S. M. *ibid.* 1960, **39**, 262.

1. Behaviour Therapy and the Neuroses (edited by H. J. Eysenck); p. 11. London, 1960.
2. Naimark, A., Brodovsky, D. M., Cherniack, R. M. *Amer. J. Med.* 1960, **28**, 368.
3. Campbell, E. J. M., Howell, J. B. L. *Brit. med. J.* 1960, i, 458.
4. Potter, E. L. *Amer. J. Obstet. Gynec.* 1946, **51**, 885.
5. Hilson, D. *Brit. med. J.* 1957, ii, 785.
6. Browne, D. *Arch. Dis. Childh.* 1955, **30**, 37.
7. Davidson, W. M., Ross, G. I. M. *J. Path. Bact.* 1954, **68**, 459.
8. Bearn, J. G. *Anat. Rec.* 1960, **136**, 107.
9. Bearn, J. G. *Arch. Dis. Childh.* 1960, **35**, 254.
10. Bearn, J. G. *Lancet*, 1959, ii, 464.

In fœtuses subjected to surgical interference—e.g., fœtal thyroidectomy, adrenalectomy, limb amputation, or eye removal—and then allowed to continue development to term within the uterine cavity, severe compression is occasionally observed and even a " snake like " appearance. This deformity occurs particularly after too much amniotic fluid has escaped during the operation, and when the incision in the uterine wall has failed to heal and allowed amniotic fluid to leak. These fœtuses survived surgical interference and continued to develop within the uterine cavity, but obvious signs of deformity were noted when they were removed just before term.

Department of Anatomy,
The Middlesex Hospital Medical School,
London, W.1. J. G. BEARN.

BLUE PENCILS FOR AUTHORS

SIR,—Letters in last week's *Lancet* on the spate of communications recalled I had once to assess a paper for publication in a society's Transactions. I reported that if the 128 pages of typescript were reduced to 25, it was acceptable. The young author was incensed, but after I spent an hour pointing out tautologies, irrelevancies, and frills, he rewrote it. It was printed, and eventually accepted for a PH.D., which certainly would not have been probable in its original state.

I read many journals, and rarely see a paper which could not be cut without loss. Although journal editors can and do sometimes shorten manuscripts, they seldom rewrite papers. One must be sympathetic to the Editor's difficulties, for to criticise a man's literary style is the surest way of rousing enmity. But it would seem practical to return accepted manuscripts to authors with a blue pencil and an invitation to use it. This would not solve the ever-growing problem but it would help.

London, S.W.3. WALTER P. KENNEDY.

P.S.—This is 57 words shorter than the first draft.

PORPHYRIA

SIR,—The subclassification and nomenclature of the disorders resulting from disturbances of porphyrin biosynthesis are in a most confused state at the moment, and your editorial of April 29 is welcomed as an endeavour to review some of the salient points. The more minutely past publications are studied the more discouraging the situation seems to become.

There is a considerable body of evidence to support a division of these disorders into distinctive groups but others prefer a " unitary hypothesis ", regarding the differences as being of no fundamental significance. The most extreme instance of the latter is the claim by Bariety et al.[1] that the findings in one of their patients virtually demolish the validity of all classifications proposed during the past 50 years. In his Chester M. Jones lecture [2] Professor Watson describes cases of hepatic porphyria from eight kindreds which present difficulties in subclassification. It is suggested that the former have ignored several unusual features in their patient which offer an alternative explanation for some of their findings. In several of the cases discussed by the latter the data are incomplete, especially with respect to fæcal porphyrin excretion, and some of the difficulties might have been resolved had this evidence been available. It is also pertinent in this connection to inquire how much support is provided for distinctive subgrouping of hepatic porphyrias by others of Professor Watson's large collection of some 270 cases.

The further studies you suggest are warmly supported, in particular an unbiased investigation of groups of patients in countries where porphyria has been shown to be reasonably prevalent—France, Italy, Argentine, &c. It is felt that patient correlation of clinical manifestations and biochemical findings is called for as well as less superficial inquiry into family incidence in the genetic forms and more thoroughgoing elucidation of possible hepatotoxic agents in the past histories of patients with the acquired type. An added complication is that each of the clinical manifestations, some of which enter into the framing of specifications of the subgroups, commonly occur in patients where the diagnosis of porphyria is not at issue. Moreover, whilst much useful diagnostic information can be gained by quite simple screening tests in the laboratory, the more elaborate procedures require a degree of proficiency only obtained by practice, and some of the techniques need methodological re-appraisal.

Careful and critical evaluation of all these features should be the basis of further study of porphyria, the first concept of which originated a little less than 100 years ago, but these disorders now clearly deserve more serious attention than they currently receive.

South African Institute for Medical Research,
Johannesburg. H. D. BARNES.

1. *Pr. Méd.* 1960, **68**, 643.
2. *New Engl. J. Med.* 1960, **263**, 1205.

NEW PENICILLINS

SIR,—Now that the nucleus of penicillin has been isolated, reports of new synthetic " penicillins ", each one masquerading under a variety of different names, will form a steady stream in our medical journals, not to mention the flow through our letterboxes in the form of advertisements. In time the wheat will sort itself from the chaff, but in the intervening period confusion is inevitable. That confusion may not be worse confounded it is vital that extravagant claims for any newcomer are not allowed to pass unchallenged.

It is for this reason that we wish to join Dr. Rolinson (April 29) in criticising the last sentence of your leading article of April 22 which states that " Like methicillin, PA-248 (α-phenoxypropylpenicillin) remains active in the presence of staphylococcal penicillinase; . . .". This is a misleading statement.

In experiments by one of us [1] it has been shown that α-phenoxypropylpenicillin is hydrolysed by staphylococcal penicillinase at one-fifth to one-half the rate of benzylpenicillin (penicillin G) depending on the concentration of antibiotic used. Under similar conditions methicillin retains almost full activity. It is thus quite untrue to suggest that α-phenoxypropylpenicillin resembles methicillin in its stability to staphylococcal penicillinase. In fact it is only slightly more stable than phenethicillin.

In terms of in-vitro sensitivity tests these findings mean that with penicillinase-producing staphylococci the results are just as much dependent on inoculum size as is the case with benzylpenicillin. We have confirmed the finding of Dr. Rolinson that, although a small inoculum of a penicillinase-producing staphylococcus is somewhat more sensitive to α-phenoxypropylpenicillin than to benzylpenicillin or phenethicillin, yet if the inoculum be large the organisms will grow in a concentration far higher than that obtainable in the tissues of a patient.

For those concerned with the treatment of patients the conclusion is obvious. Methicillin has proved to be life-saving in the treatment of staphylococcal septicæmias due to penicillinase-producing organisms and is now the drug of choice for all severe penicillin-resistant staphylococcal infections. For such cases α-phenoxypropylpenicillin is not a serious rival.

Postgraduate Medical School of London,
London, W.12. MARY BARBER.

National Institute for Medical Research,
London, N.W.7. RICHARD NOVICK.

*** Some readers may suppose from our correspondents' concluding remarks (and the earlier comments of Dr. Rolinson) that our ill-judged phrase was part of an

1. Novick, R. P. Unpublished data.

assault on the merits of methicillin. In fact we said: "Its active bactericidal properties and lack of toxicity make it drug number one for all severe staphylococcal infections resistant to penicillin."—ED. L.

SIR,—Dr. Thomsen's comments (May 6) on the possible fallacies of comparing single determinations of serum levels of antibiotics must be of considerable interest and importance to all concerned with the assessment of new antibiotics.

Surely, however, the greatest fallacy is the contention that the time of so-called "peak" serum levels can be measured, in a small number of individuals, with the degree of accuracy inferred by Dr. Thomsen and the results thereafter extrapolated to the population at large. The point is well illustrated by a study of the individual figures from which the times of peak levels quoted by Dr. Thomsen are derived—viz., "about half an hour" with penicillin V and "half to one hour" in the case of phenethicillin.

In the studies by Juncher and Raaschou,[1] to which Dr. Thomsen refers, peak serum levels of penicillin V were studied in blood samples from 10 subjects withdrawn quarter of an hour, half an hour, one hour, and two hours after administering the antibiotic. The highest mean figure of serum concentration for these 10 subjects occurred at half an hour, when a level of 2·9 μg. per ml. was recorded. But the individual observations from which this mean was calculated varied between a "trace" and 8·6 μg. per ml. The lower (95%) confidence limit of this mean is 1·35. Moreover, in 5 of these 10 subjects the peak level actually occurred at one hour or later (in 2 of the 5 at two hours). In a further 3 the peak occurred at half an hour, while in the remaining 2 subjects the quarter-hour and half-hour levels were identical, but greater than the one-hour level. The mean values at quarter of an hour and at one hour were 2·4 and 2·5 respectively, compared with a half-hour mean of 2·9. This latter figure is, it should be noted, only approximately 19% above the quarter-hour or one-hour mean, but is, none the less, quoted as the time at which the peak serum concentration occurs. Little reliance can be placed on this deduction when it is realised that, in fact, 50% of the subjects registered a peak level at one hour, and that the lower confidence level of the half-hour mean lies appreciably beyond both the quarter-hour and one-hour means.

In the case of phenethicillin, Knudsen and Rolinson [2] examined the times of individual peak serum concentrations in 3 subjects and recorded figures of 50 min., 60 min., and 90 min., thereby confirming the considerable individual variation in the time of peak levels.

It is abundantly clear that the time of highest average serum concentration in a small number of test subjects does not indicate the time at which peak levels *most frequently* occur in these subjects. In these circumstances, therefore, it may be submitted that measurement of levels at one hour is likely to provide relative figures as accurate as measurements at quarter of an hour, half an hour, or two hours, or indeed as measurements at times which are different for all three penicillins—on the assumption (which it would appear is erroneous) that these different times necessarily reflect the behaviour of the "average" subject.

Finally the relative merits of these 3 penicillins, in terms of the ratios of serum levels which they provide, have not been assessed by "only a single determination of the serum concentration". The two-hour and four-hour levels which were also presented give ratios similar to the one-hour values.

Our conclusions, therefore, on the relative merits of these 3 penicillins remain unaltered.

Clinical Research Department,
Pfizer, Ltd.,
Sandwich, Kent. J. K. MORRISON.

SIR,—Mr. Lightbown (May 6) takes us to task over the validity of "apparent loss %" of antibacterial activity of semisynthetic penicillins in vivo. He suggests that our results merely "demonstrate the discrepancies that are found when the 3 preparations are compared against benzylpenicillin under slightly different conditions". With this view we do not agree.

The amount of an antibiotic in a sample of serum can be measured in terms either of the antibiotic itself (as advocated by Garrod [1]), or of a representative of the group (as carried out for the tetracyclines by Kunin et al.[2]). It is our belief that these two methods are complementary when applied to the *same* sample of serum, and give, however imperfectly, the only guide to what might indeed be taking place within the human body. To combine these two methods and compare the results so obtained, in an attempt to elucidate the problem, has as far as we are aware not previously been attempted. It is with this attempt that Mr. Lightbown is in disagreement.

The figures quoted are all based upon experiments carried out either at the same time (in the case of the serum assay studies), or upon the same solid samples of the various semisynthetic penicillins (for the figures given for their activity expressed in terms of international units of benzylpenicillin). The criticism that the techniques and standards used were not "international" would to us seem irrelevant, since the figures obtained for biopotency were determined in the laboratory, and the same figures were used for the reverse calculation of the weight of available antibiotic. Thus, the absolute accuracy of the figures for biopotency, the test organism used, and the environmental factors are unimportant, since they were identical in both phases of the experiments.

The discrepancy between the calculated weight based on antibacterial activity of the serum sample and the actual weight can, therefore, give a rough guide to the effect of body fluids—in this case serum—upon the activity of the semisynthetic penicillins under test. This would seem very desirable, since we now know that many penicillins, unlike benzylpenicillin, are adversely affected in vitro by the presence of serum within the culture medium (Gourevitch et al.[3 4]). In view of this we believe that the serum values for a semisynthetic penicillin obtained from assay against its own standard may be misleading in the interpretation of the results of comparative blood studies. Our approach is an attempt to overcome this difficulty.

Finally, it should be emphasised that Mr. Lightbown's criticism does not affect our conclusions regarding the relative merits of the 3 oral penicillins, since these conclusions were primarily based (as advocated by Garrod [1]) upon a consideration of in-vitro activity together with weight concentrations in the serum.

Clinical Bacteriology Research Department,
Pfizer, Ltd.,
Sandwich, Kent. G. M. WILLIAMSON.

AN ADVERTISEMENT

SIR,—I wish to call your readers' attention to what appears to me to be the dangerous and unethical advertising of a preparation called 'Elestol' for "the treatment of rheumatoid arthritis, muscular rheumatism and osteoarthritis".

In the advertisements in journals issued to general practitioners it is described as containing "chloroquine phosphate and symptomatic components" (*Monthly Index of Medical Specialities*, April, 1961). In the folders sent by mail to practitioners with a brief description of the indications and comment on the safety of the preparation, it is possible to discover that it contains sufficient prednisone to give 4 mg. per day at the recommended dose as well as 1·2 g. (gr. 20) of aspirin.

As the preparation is recommended for long-term use, I feel its content of prednisone should be clearly stated in all advertising literature. No mention is made of the permanent

1. Juncher, H., Raaschou, F. *Antibiot. Med.* 1957, **4**, 497.
2. Knudsen, E. T., Rolinson, G. N. *Lancet*, 1959, ii, 1105.

1. Garrod, L. P. *Bull. Hyg., Lond.* 1960, **35**, 384.
2. Kunin, C. M., Dornbush, A. C., Finland, M. *J. clin. Invest.* 1959, **38**, 1950.
3. Gourevitch, A., Hunt, G. A., Lein, J. *Antibiot. and Chemother.* 1960, **10**, 121.
4. Gourevitch, A., Hunt, G. A., Lein, J. *Antibiot. Ann.* 1959–60, p. 111.

ocular damage which may arise from the long-term use of chloroquine in this dose.

Belfast. P. C. ELMES.

HOSPITAL DOCTORS

SIR,—I am almost grateful to Dr. Smith (May 6) for asking why, as a time-expired senior registrar, I feel constrained to write anonymously. I still find myself, in spite of maturity, qualification, and experience, to be dependent on the goodwill of my seniors and all their colleagues of the appointment committee which I still presume will eventually accept me. My confidence in equity within the profession has unfortunately suffered considerably in a decade, and selfconfidence, carefully guarded in respect of professional work, has also taken a considerable battering.

Those in my position have found that our seniors have not been able to see clearly enough to be prepared to give the advice which we have sought. Faced with the preoccupation of placing our colleagues from teaching hospitals, the senior members of the profession have not been able to solve the difficulties of those holding the disadvantageous positions. It would be unrealistic not to recognise the potency of such pressures.

With a firmly established prototype for professional advancement and a massive and unequal competition for consultant appointments it would not be politic for any senior registrar to face personal criticism from just those people who have his future in their hands, and to risk being regarded as a troublemaker. The professional interests of the established and the non-established doctor within the hospital service are, unfortunately, often opposed.

I am endeavouring, Sir, not to make judgment nor to be bitter. Were I secure and confident that I could continue building up my professional work on a long-term basis it would be my pleasure to be altruistic and to allow myself the luxury of expressing political views based on belief. As it is I must continue to keep myself as impersonal as possible against the day when I no longer have to seek the anonymity of

TIME-EXPIRED SENIOR REGISTRAR.

NEUROBLASTOMA AND CATECHOLAMINE EXCRETION

SIR,—The determination of urinary metabolites of noradrenaline and, in particular, 3-methoxy-4-hydroxymandelic acid (vanil mandelic acid, V.M.A.) in patients with neuroblastoma is attracting interest.

In a series of 5 cases, Voorhess and Gardner [1] included 1 in which there was no increase of noradrenaline or V.M.A. We have recently examined urine from 3 children with histologically proven neuroblastoma; in 1 there was a considerable increase in V.M.A. excretion, but in the other 2 there was no gross increase, as measured both by the screening method of Gitlow et al.[2] and by paper chromatography. But a large amount of free dopamine (3-hydroxytyramine) was found in the urine of these 2 children. A striking increase in the total catecholamine excretion was detected by a modification of the method of Bell et al.,[3] while the adrenaline + noradrenaline levels, as measured by ferricyanide oxidation of the same eluates, were less than 0·1 and 0·2 μg. per mg. of creatinine respectively. The corresponding figures for dopamine ranged from 20 to 120 μg. per mg. of creatinine in one case, and 215 to 230 μg. in the other; and phenolic-acid chromatograms showed the presence of appreciable amounts of homovanillic acid (a metabolite of dopamine) as well as other unidentified substances.

1. Voorhess, M. L., Gardner, L. I. *J. clin. Endocrin.* 1961, **21**, 321.
2. Gitlow, S. E., Ornstein, L., Mendlowitz, M., Khassis, S., Kruk, E. *Amer. J. Med.* 1960, **28**, 921.
3. Bell, M., Horrocks, R. H., Varley, H. cited *in* Varley, H. Practical Clinical Biochemistry; p. 528. London, 1958.

The excretion in 14 other children who had, or had had, a variety of tumours was also determined. These comprised 7 children (2 with Ewing's tumours, 2 with medulloblastomas, 1 with a Wilms tumour, 1 with a retinoblastoma, and 1 with Hand-Schüller-Christian disease) with tumour active at the time of examination, and 7 children (5 with neuroblastomas and 2 with Ewing's tumours) previously treated and in whom there was no evidence of recurrence. The total catecholamine excretion (as dopamine) in these 14 children has ranged from 0·3 to 1·3 μg. per mg. of creatinine.

These observations suggest that in patients with suspected neuroblastoma the determination of V.M.A. alone, or of this substance and noradrenaline, may not be sufficient to confirm the diagnosis; but the possibility of success would be greatly increased by combining the method of Gitlow et al.[2] with a method for catecholamine assay which also measures dopamine. The simplest method is the one we used in our investigations, which combines the absorption of amines on to 'Amberlite IRC 50' with the ethylenediamine reaction for catechols. By using a suitable source of ultraviolet light, visual screening is possible. Though the method is relatively crude, since the three catecholamines show differential fluorescence, this is not such a great disadvantage in this context, where there appears to be scarcely any reacting material present other than dopamine, as in phæochromocytoma (15 confirmed cases examined since 1956). But we should remember that even these tests would be negative if the metabolic sequence was interrupted before dopamine was reached.

Department of Clinical Pathology, Manchester Royal Infirmary. MAURICE BELL.

Children's Tumour Registry, Departments of Child Health and Pathology, Manchester University. J. K. STEWARD.

HUMAN RELATIONS IN HOSPITAL

SIR,—Many of your readers will welcome the letter of Dr. MacSorley (April 29) on this important subject. I believe that the medical profession will have to develop a new attitude to the patient who criticises the hospital service, for at present our first reaction is one of self-justification. Having done the best we can for the patient, maybe at some cost to our personal convenience, we tend to feel that the appropriate emotion for him to register is one of gratitude. We have, however, come into medicine quite freely and we are, nowadays, reasonably paid for our services. There is a sense in which we must be prepared to forgo our traditional immunity from criticism and set out to give, as Dr. MacSorley says, satisfaction to our customers.

There is a tendency to label anyone who is critical as "ungrateful". This is unfair. A patient may be profoundly thankful for skilful attention and recovery of health and, at the same time, wish to make some necessary and valuable criticisms of the hospital service. A lady whom I know was recently in hospital for the birth of her baby and received excellent care. She was, however, appalled at the dirtiness of the lavatories. This patient made no complaint about a serious lapse in hospital hygiene because she did not wish to distress the sister or appear ungrateful. There should be a way in which this patient could have made an objective and useful comment on the practical organisation of the hospital. This is probably where a ward suggestion-box would help the diffident.

There will be more difficult occasions when the personal handling of a patient is open to some criticism. The article in *The Spectator* from which Dr. MacSorley quotes is an example. There had clearly been a serious breakdown of personal relationships between the writer and her hospital attendants. I think we should feel considerable disquiet that, as a result, an article making damaging allegations against surgeons as a body should be published under the title Hospitals versus Patients.

This suggests that there are patients who leave hospital feeling that they have been treated with insufficient respect, and that their welfare has been subordinated to that of members of staff. Some patients may have reason to feel as they do. On the other hand, attendance at hospital will always be a transaction in which emotions are deeply involved, and the anxious patient and relative is not always as reasonable and balanced as he would normally be. Even small failings in the hospital staff can cause disproportionate distress, and misunderstandings are likely to arise, usually through failure of staff to explain hospital procedure.

A steady concern for the patient and his family is something which must be nurtured in a hospital staff, and only in this way can relationships be improved. I think that Dr. MacSorley's suggestion of a meeting of interested people could help considerably in the diffusion of this concern. I think he is right in wishing to avoid a set committee and he is certainly right in welcoming the younger members of the staff—I hope this would include junior nurses and that they would be encouraged to participate. Almoners should be particularly valuable attenders.

Special thought should be given to this whole subject in children's hospitals, where it is not easy to know what can reasonably be demanded of young and inarticulate patients: consideration could, for instance, be given to the proper conduct of minor procedures which cause discomfort and pain.

If we can be humane and reasonable in our attitude to criticism we shall give no encouragement to frivolous or unreasonable complaints. It will, however, make it easier for those who want to improve the hospital service by intelligent comment to come forward.

Aberdeen. PETER F. JONES.

CHLORHEXIDINE AND *Proteus rettgeri* INFECTION

SIR,—We should like to make the following observations on the communication by Dr. Lubsen and others in your issue of April 29:

1. The authors state that *Proteus rettgeri* is very resistant to antibacterial agents. There is no evidence that resistance to chlorhexidine has developed in their wards.

2. The authors' tabulated results show that for 11 of 15 strains of *Pr. rettgeri* tested, the minimum bactericidal concentration of chlorhexidine was 1/8000 or less; this hardly justifies their generalisation in the text that "the growth of *Pr. rettgeri* is not inhibited by the concentration of chlorhexidine ('Hibitane') used in our urological ward (i.e., 1/5000)", and indeed had a 1/5000 concentration been included in the test dilutions it might well have been that 14 of these 15 strains would have been inhibited by it.

3. Infections with *Pr. rettgeri* apparently did occur before 1957, and the authors only "assume" that the subsequent increase in them was due to chlorhexidine.

4. It is well recognised that many factors contribute to the occurrence of infections in genitourinary wards (see, for example, Pyrah et al.[1]), and it is unreasonable to rely solely upon any antiseptic to control them all. Chlorhexidine is widely used in genitourinary wards and has been shown [2–6] to have an important place in an integrated scheme of control measures.

1. Pyrah, L. N., Goldie, W., Parsons, F. M., Raper, F. P. *Lancet*, 1955, ii, 314.
2. Gillespie, W. A., Lindon, K. P., Miller, A., Slade, N. *J. clin. Path.* 1960, **13**, 187.
3. Gillespie, W. A. *ibid.* 1961, **14**, 26.
4. Miller, A., Gillespie, W. A., Linton, K. B., Slade, N., Mitchell, J. P. *Lancet*, 1960, ii, 886.
5. McLeod, J. W. *ibid.* 1958, i, 394.
6. Paterson, M. L., Barr, W., Macdonald, S. *J. Obstet. Gynæc. Brit. Emp.* 1960, **67**, 394.

On the evidence presented, we submit that Dr. Lubsen and his colleagues do not justify either the title of their communication or the generalisation in their last sentence.

G. E. DAVIES
A. R. MARTIN
G. SWAIN
F. L. ROSE
Research Department.
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Parliament

Expenditure on Social Services

THE figures below cover expenditure on education, child care, school meals and milk, welfare foods, health services, National Insurance, National Assistance, war pensions, non-contributory pensions, and family allowances, and housing. To avoid double counting, grants from the Exchequer to the National Insurance Funds and to local authorities are excluded from the figures given for Central Government expenditure.

	£ million	
	1959–60	1960–61
Central Government:		
Current expenditure	1212	1337
Capital expenditure	54	60
National Insurance funds:		
Current expenditure	1034•	1089•
Local authorities:		
Current expenditure	1007†	1097†
Capital expenditure	400	397
Total, all authorities, current and capital	3707	3980

• Grants from the Exchequer to the National Insurance funds were £185 million in 1959–60 and £187 million in 1960–61.
† Grants from the Exchequer to local authorities, mainly in respect of social services expenditure and housing, totalled £565 million in 1959–60, and £658 million in 1960–61.

Total current and capital expenditure by all public authorities on social services and housing in 1960 is estimated at about 17·5% of the gross national product (at factor cost). The corresponding figure for 1959 was 17·3%.

QUESTION TIME

Hospital Admissions under Mental Health Act

Baroness WOOTTON OF ABINGER asked, in the event of an application for admission to a hospital being made under sections 25, 26, or 29 of the Mental Health Act, 1959, what were the rights of a hospital to refuse to admit such a patient; and upon whom did the obligation lie to make the arrangements required by subsection 3 of section 60 of the Act, and what were the rights of a hospital to decline to be the hospital specified in an order under section 60 of the Act.—Lord NEWTON replied: The Mental Health Act does not define the duties of hospitals in regard to the admission of patients. But regional hospital boards have been asked to ensure that, whatever the admission procedure, psychiatric emergencies are admitted immediately, and that patients requiring treatment less urgently are admitted with due regard to the accommodation available and to their need for admission. The Minister of Health has indicated that it is for one of the two doctors whose evidence is needed for the purposes of section 60 to make the arrangements required by subsection 3 of that section.

Baroness WOOTTON OF ABINGER: Is the noble Lord satisfied that these arrangements are working smoothly; in particular, that there is no delay in the admission of patients; and that there is no danger of patients being, so to speak, "hawked around" from one hospital to another in an attempt to gain admission? Can he assure the House that a court cannot find itself in the position of being unable to make a hospital order simply because no hospital can be found which is willing to accept the patient?—Lord NEWTON: There could be circum-

stances in which a hospital could not be found to take a patient who the court thought should be ordered to go into hospital. But the Minister knows of only one case in which there has been difficulty.

Lord LINDGREN: Would not the noble Lord agree that the difficulty that has occurred arises from the phrasing he himself has used: urgency and less urgency? Differences of opinion, even in the medical profession, arise on the question of "less urgency".—Lord NEWTON: I imagine that there are differences of opinion within the medical profession, as within any other profession. But it was a deliberate provision in the Act that the order of admission should be determined by need, and not by the type of admission procedure: because a patient who is willing to go into a mental hospital as an informal patient may well be in more urgent need of treatment than another patient in respect of whom compulsory powers have been used.

Safety in Operating-theatres

Mr. L. ABSE asked the Minister of Health whether he was aware that a report had been received by the Newport and East Monmouthshire hospital management committee from their consultant surveyor stating that conditions at the twin operating-theatres at the Royal Gwent Hospital are hazardous and are not up to safety standards; whether he was aware that the hospital management committee has protested to the Welsh Regional Hospital Board at delays in providing new theatres; and what action he intends to take to end the existing hazards.—Miss EDITH PITT replied: I understand that one of the consultant surgeons expressed himself in this sense at a meeting of the committee. An officer from the Welsh Board of Health is to visit the theatres immediately with representatives of the Welsh Hospital Board, and report their conclusions. Mr. ABSE: Is not the Parliamentary Secretary aware that for more than six months the management committee has been pressing this problem with the Ministry? Why is it that we have had to wait until there has been a report which the chairman of the hospital management committee has rightly said will have a frightening effect on folk before the Ministry even takes the trouble to go there and inspect the actual circumstances?—Miss PITT: It is true that the hospital management committee has been pressing this point. There are proposals for the rebuilding of the hospital. In the meantime, however, in view of the representations, the matter is being looked at very urgently.

Maternity Protection

DAME IRENE WARD asked the Minister of Labour when it was his intention to ratify convention no. 103 of the International Labour Organisation concerning maternity protection.—Mr. JOHN HARE replied: The position remains as stated in Cmnd. 9082 presented to the House in March, 1954, and the Government do not propose to ratify this convention. DAME IRENE WARD: I agree that, fundamentally, these matters are better settled between employer and employee, on a voluntary basis, but what does the member suggest can be done when the employer and the employed fail, perhaps, to carry out what are, I think, the accepted arrangements when there are maternity cases involved in employment?—Mr. HARE: I agree that this is primarily a matter best settled between the employer and worker. This convention does not guarantee an expectant woman against dismissal. It is a very difficult problem which in the ordinary way can be settled properly only by good sense in the relationship between employer and employee. Mrs. BARBARA CASTLE: As there are employers, including, unfortunately, the Press Association, who are still following the barbaric practice of dismissing married women employees who have been with them for 15 years simply because they have become pregnant, does not the Minister think that the time has come for us to follow the example of France and to give protection to the right of reinstatement of married women by law as is done in that country?—Mr. HARE: I think that that would be very difficult. I understand the hon. Lady's feeling about this, but, once we start legislating, we are in danger of prejudicing the position of married women and of putting them under restraints which would make life more difficult for them than it is at the moment.

Cost of Collecting N.H.S. Contributions

Mr. J. T. PRICE asked the Minister of Pensions and National Insurance why the cost of the collection of the National Health Service contributions in 1961–62 was expected to rise from £850,000 to £1,583,000.—Mr. A. BOYD-CARPENTER replied: The main reasons are the changes in the National Health Service contribution-rates and in the accounting arrangements of the General Post Office as a result of which Post Office costs are met initially from my department's vote, and not, as hitherto, directly from the proceeds of the contributions.

Diary of the Week

MAY 14 TO 20

Monday, 15th

UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Prof. A. Engström (Stockholm): Micro X-ray Analysis Applied to Biology and Medicine. (First of three lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Alcohol Addiction.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) Prof. Hallowell Davis (St. Louis, Missouri): Relation of Presbycusis to Noise-Induced Hearing Loss.
9 P.M. *General Practice.* Dr. Jean Broughton: Growing Up in Manchester. (Presidential address.)

Tuesday, 16th

UNIVERSITY OF LONDON
5.30 P.M. (King's College.) Professor Engström: Bone as a Problem in Molecular Biology. (Second of three lectures.)
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. D. N. Menzies: Uses of Oxytocin in Obstetrics.

Wednesday, 17th

UNIVERSITY OF LONDON
5.30 P.M. (King's College.) Professor Engström: Dose-damage Relationship for Internal Contamination with Radioisotopes. (Last of three lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. B. P. Marmion: Aspects of Viral and Rickettsial Pneumonias in Man.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Comparative Medicine.* Dr. J. L. Stafford, Dr. D. J. Perkins: Iron Metabolism.
8.15 P.M. *General Practice.* Sir George Schuster: Cooperation between General Practitioners and the National Health Service.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Prof. E. I. Grin: Control of Tinea Capitis.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. Donald Barlow: Difficulty in Swallowing.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. J. A. L. Gilbert (Edmonton, Alberta): After Gastrectomy.
UNIVERSITY OF OXFORD
5 P.M. (Dyson Perrins Laboratory.) Prof. F. G. Young: Research on Diabetes Mellitus. (Litchfield lecture.)

Thursday, 18th

UNIVERSITY OF LONDON
5.30 P.M. (King's College.) Prof. N. Jancsó (Szeged, Hungary): Inflammation and Inflammatory Mechanisms.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Lilian Recant: Oral Hypoglycæmic Agents.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. Stafford: Modern Trends in the Theory and Practice of Blood Transfusion.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. W. E. Ormerod: Study of Volutin Granules in Trypanosomes.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Mr. Ralph Shackman: Acute Renal Failure.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Prof. P. Lacroix: Healing of Fractures.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Dr. C. H. Burnett (University of North Carolina): Resistant Rickets—some Genetic, Diagnostic, and Therapeutic Problems.

Friday, 19th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. D. N. Walder: Blood Flow.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. D. F. N. Harrison: Tonsil and Adenoid Problems.

Notes and News

INSTITUTE OF VIROLOGY IN GLASGOW

ON May 4 the Institute of Virology in the University of Glasgow was opened by Sir John Erskine, chairman of the Scottish Hospital Endowments Research Trust, which granted £237,000 to meet the cost of the building and its major equipment and of its first two years of academic activity. The Institute houses the university department of virology (the first in Britain) and the Medical Research Council Experimental Virus Research Unit, both of which are in the charge of Dr. Michael Stoker, professor of virology in the university.

An electron microscope and dark rooms are located in the basement. On the ground floor are glass-washing, preparation, and sterilising rooms, and a connection gives access to the animal house. The first and second floors contain the main laboratories and research rooms, cold rooms, hot rooms, and sterile rooms. Administration rooms, library, and colloquium and quiet rooms are on the third floor.

The aim is to create a postgraduate teaching and research centre for basic virology, and to develop, in a modest way, the teaching of virology to undergraduates. It is hoped to develop virology as a subject for science students, closely linked to biochemistry, genetics, and science bacteriology, and leading to an honours class in virology. In addition, an advanced postgraduate course in basic virology is being held in conjunction with a similar course in cell biology. The research will be concerned mainly with the nature of viruses, their mode of growth, and their effects on individual cells. At present attention is being devoted to viruses which cause long standing infections, and to the changes which these viruses may produce in the hereditary structure of the host cells.

The Institute is close to related departments in the university, and to the Western Infirmary for which it will provide diagnostic facilities; but the laboratory diagnosis of virus diseases in the city will continue to be centred on the laboratories at Ruchill Hospital and at Belvidere Hospital.

RESEARCH INTO DIABETES

DIABETIC associations have grown up in several countries. In some they are composed predominantly of doctors, in others of patients: in few does there seem to be a balance between the two. There are many things for a diabetic association to do—to promote, encourage, and organise medical research and to help patients with problems of diet, employment, and geriatric care. There is ample room for both approaches, yet it seems that most of the national organisations lean heavily either to the medical or to the social side.

The British Diabetic Association was founded by R. D. Lawrence just over a quarter of a century ago. Its membership is largely of patients, but it has always included some doctors. Just over a year ago the Association set up a medical and scientific section to comprise doctors and science graduates interested in the varied problems of diabetes. There are now nearly 350 members of the section, whose chairman is Prof. F. G. Young.

Since the inaugural meeting in April, 1960, two others have been held. The first was at Glasgow last October when a symposium on pre-diabetes was held. This provided a valuable survey of this strange condition—the sole "disease" which can be diagnosed with certainty only in retrospect—and led to the setting up of a small group to study the possibility of organising prospective trials of the prophylactic value of various treatment regimens. If the occasional appearance of retinal damage at the time when diabetes is first diagnosed is due to the condition having been present for some time unrecognised, then anything that can prevent or even postpone its development is valuable. The section has also started to study the techniques of prevalence surveys. This deliberate preliminary study is necessary before launching detection drives to discover the undiagnosed diabetics, who it seems may be as numerous as known diabetics.

The medical and scientific section now meets twice a year. The meeting last month at University College Hospital brought forth a group of papers on biochemistry and clinical medicine of a high level. The autumn meeting at Birmingham is to include a symposium on diabetic kidney disease, and the first reports of the comprehensive survey of the prevalence of diabetes among 25,000 patients by the Birmingham faculty of the College of General Practitioners. Next spring the section will meet at the Postgraduate Medical School of London when the symposium will be on pituitary ablation and other endocrine procedures in the treatment of the so-called complications of diabetes.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Amitriptyline	3-(3-Dimethylaminopropylidene)-1:2-4:5-dibenzo-*cyclo*hepta-1:1-diene Tryptizol is the hydrochloride
Chlorphedianol	1-*o*-Chlorophenyl-3-dimethylamino-1-phenyl-propan-1-ol Detigon is the hydrochloride
Chlormezanone	2-*p*-Chlorophenyltetrahydro-3-methyl-1:2-thiazin-4-one 1:1-dioxide Trancopal
Chlorquinol	A mixture of the chlorinated products of 8-hydroxyquinoline containing about 65 per cent of 5:7-dichloro-8-hydroxyquinoline Quixalin
Cyclopenthiazide	6-Chloro-3:4-dihydro-3-*cyclo*pentylmethyl-7-sulphamoylbenzo-1:2:4-thiadiazine 1:1-dioxide Navidrex
Cyproheptadine	1-(1:2-5:6-Dibenzo*cyclo*heptatrienylidene)-4-methylpiperidine Periactin is the hydrochloride
Dextrothyroxine	D-α-Amino-β [-4-(4-hydroxy-3:5-di-iodophenoxy)-3:5-di-iodophenyl] propionic acid Choloxin is the sodium salt
Emylcamate	1-Ethyl-1-methylpropyl carbamate Striatran
Ethamivan	*NN*-Diethylvanillamide Vandid
Ethebenecid	*p*-Diethylsulphamoylbenzoic acid Urelim
Hexadimethrine Bromide	Poly-(*NN'N'N* -tetramethyl-*N*-trimethylenehexamethylenediammonium dibromide) Polybrene
Homochlorcyclizine	1-(*p*-Chlorobenzhydryl)-4-methylhomopiperazine
Hydrargaphen	Phenylmercury 2:2′-dinaphthylmethane-3:3′-disulphonate Penotrane
Interferon	A protein formed by the interaction of animal cells with viruses capable of conferring on animal cells resistance to virus infection.
Iophendylate	Ethyl 10-*p*-iodophenylundecanoate Ethiodan; Myodil
Methamphazone	4-Amino-6-methyl-2-phenyl-3-pyridazone
Methyclothiazide	6-Chloro-3-chloromethyl-3:4-dihydro-2-methyl-7-sulphamoylbenzo-1:2:4-thiadiazine 1:1-dioxide Enduron
Morazone	2:3-Dimethyl-4-(3-methyl-2-phenylmorpholino-methyl)-1-phenylpyrazol-5-one
Noxythiolin	*N*-Hydroxymethyl-*N'*-methylthiourea
Phenoxypropazine	(1-Methyl-2-phenoxyethyl)hydrazine Drazine is the hydrogen maleate
Phentermine	αα-Dimethylphenethylamine Duromine (an ion-exchange resin complex)
Phenyltoloxamine	*o*-Benzylphenyl 2-dimethylaminoethyl ether
Pivazide	*N*-Benzyl-*N*[1]-pivaloylhydrazine Tersavid
Polynoxylin	Poly[methylenedi(hydroxymethyl)urea] Anaflex
Propatylnitrate	1:1:1-Trisnitratomethylpropane Etrynit; Gina
Pseudoephedrine	(+)-2-Methylamino-1-phenylpropan-1-ol (a stereoisomer of ephedrine)
Sorbide Nitrate	1:4-3:6-Dianhydrosorbitol dinitrate
Viprynium Embonate	6-Dimethylamino-2-[2-(2:5-dimethyl-1-phenyl-3-pyrrolyl)vinyl]-1-methylquinolinium embonate (Embonic acid is adopted as the trivial name for 4:4′-methylenebis-(3-hydroxynaphthalene-2-carboxylic acid)) Vanquin
Xanthocillin	Antibiotics obtained from the mycelium of *Penicillium notatum* (Zanthocillin X is 2:3-Di*iso*cyano-1:4-di(*p*-hydroxyphenyl) buta-1:3-diene)

Proprietary name	*Approved name*
Anaflex	Polynoxylin
Choloxin	Dextrothyroxine
Detigon	Chlophedianol
Drazine	Phenoxypropazine
Duromine	Phentermine
Enduron	Methylcothiazide
Ethiodan	Iophendylate
Etrynit	Propatylnitrate
Gina	Propatylnitrate
Myodil	Iophendylate
Navidrex	Cyclopenthiazide
Penotrane	Hydrargaphen
Periactin	Cyproheptadine
Polybrene	Hexadimethrine Bromide
Quixalin	Chlorquinol
Striatran	Emylcamate
Tersavid	Pivazide
Trancopal	Chlormezanone
Tryptizol	Amitriptyline
Urelim	Ethebenecid
Vandid	Ethamivan
Vanquin	Viprynium Embonate

EMPIRE RHEUMATISM COUNCIL

AT the annual meeting of the Council held in London on May 4, Dr. W. S. C. Copeman, the chairman, spoke of the transformation in the attitude towards rheumatism since the Council was founded twenty-five years ago. In the past ten years the money which the Council spent on medical research had risen from under £5000 to over £56,000, including covenants of £10,000 each from Sir Edward and Lady Lewis. He announced a new gift of £30,000 received from Mr. R. F. Macfarlane.

Dr. Copeman remarked that, though experts have always suspected that more people suffer from arthritis than is generally supposed, they have been startled by figures from the first comprehensive population survey ever made in rheumatism, which was carried out by the Council's mobile field unit. Summarised in the annual report [1] the first results published in the *Annals of Rheumatic Diseases* (1961, **20,** 11) suggest that in the United Kingdom at any one time at least 1,400,000 people have rheumatoid arthritis. In one person out of ten, changes caused by osteoarthritis begin to appear at the age of 24; and at 65 nearly a third of the population (nearly $3^3/_4$ million people) have osteoarthritis—moderate or severe.

The Council has pursued its policy of providing information for the general practitioner. During the past year its "Reports on Rheumatic Diseases", distributed to all practitioners free of charge, have included one on the use of steroids and one on cervical disc lesions; and a handbook for the parents of children with rheumatic fever was published.

Sir Charles Dodds spoke on the complexity of research on the rheumatic diseases and Dr. A. G. S. Hill on recent research by the Council.

HYPOTHERMIA

AT a meeting on May 6 of the Faculty of Anæsthetists of the Royal College of Surgeons of England, Dr. GEOFFREY ORGANE, the dean of the Faculty, indicated the confusion that had arisen through the application of different criteria and techniques of hypothermia in different centres. He raised the problem of temperature differentials in various parts of the body: few opportunities arose of directly measuring brain temperature, which might well be considerably higher than œsophageal.

Prof. ERIC NEIL regretted the distraction caused by the interest in hibernants from the experimental attack on the physiological problems of hypothermia. Much of the energy directed to the study of hypothermia had been expended in analysing the changes produced by simple cooling and rewarming, but the surgeon employed hypothermia as an adjunct to local or general circulatory occlusion. Clamping the venæ cavæ raised central venous pressure, and the splanchnic organs were thereby exposed to a combination of venous congestion and progressive anoxia during the period of circulatory occlusion. He stressed the limitations in applying the results of observations on normal dogs to diseased man, and the importance of acid-base equilibrium: in our present state of knowledge a pCO_2 of 40 mm. Hg, even in hypothermia, should be taken as normal.

Mr. C. E. DREW described the apparatus and technique used to induce profound hypothermia in cardiac surgery. Of 110 patients 44 required electrical defibrillation. Electroencephalography was of little use at body-temperatures below 20°C. Insufficient cooling of the brain and air embolism remained the greatest dangers. No regional temperature should be allowed to fall below 10°C. Symptoms of brain-stem damage might not appear for three to four days.

Mr. L. S. WALSH, discussing hypothermia in cerebral surgery, said that reduced blood-flow to the entire brain, or part of it, was better tolerated than at normal temperatures, and hypothermia was used by him routinely in the surgery of aneurysms and other vascular tumours in which there was always a danger of sudden blood-loss. It was difficult to be certain to what extent hypothermia could mask the signs of cerebral compression. There was as yet no convincing evidence of the value of hypothermia in the treatment of cerebral neoplasms.

Dr. DAVID MENDEL discussed acid-base balance in hypothermia. On cooling, the blood-pH remained unaltered if the pCO_2 to which the blood was exposed remained unchanged. A change of pH during hypothermia could be due to either the pCO_2 or the amount of "fixed" acid or alkali in the blood having changed. It was important that cerebral blood-flow be maintained: the arteriovenous pH difference was an indication of its adequacy. He agreed with Professor Neil that keeping the pCO_2 at 40 mm. Hg assured in general an adequate cerebral blood-flow by its effect on the cerebral vascular resistance.

1. Obtainable from the Council at Faraday House, 8, Charing Cross Road, London, W.C.2.

HOSPITAL INPATIENT INQUIRY

THE first part of the report on the Hospital Inpatient Inquiry for 1959 [1] gives summaries for selected conditions for 1959 and certain figures for 1955–59 which will be amplified in part II.

The survey is based on a 10% sample of discharges (including deaths) from National Health Service hospitals. Discharges in 1959 totalled 3,664,100 (807·3 per 10,000 population), compared with 3,554,700 (788·0 per 10,000) in 1958—an increase of 2·4%.

2200 cases (0·5 per 10,000) of acute poliomyelitis were discharged, 1000 fewer than in 1958. There was a steady rise in cancer of the lung—from 22,400 (5·0 per 10,000) in 1955 to 30,600 (6·7 per 10,000) in 1959. Discharges of patients with ischæmic heart-disease numbered 56,600 in 1959 (12·5 per 10,000)—6800 more than in 1958. 60·5% of women were delivered in hospital compared with 57·5% in 1958.

1. Ministry of Health and General Register Office: Report on Hospital Inpatient Enquiry for 1959, Part I. H.M. Stationery Office. 1961. Pp. 16. 1s. 6d.

University of Leeds

On May 18 the honorary degree of D.SC. will be conferred on Prof. C. H. G. Macafee.

University of Glasgow

Dr. J. F. Boyd has been appointed senior lecturer in pathology of infectious diseases, Dr. H. M. McCallum lecturer in pathology at the Western Infirmary, and Dr. J. Gordon lecturer in bacteriology at the Western Infirmary.

Royal College of Physicians of Edinburgh

At a meeting on May 2, with Dr. J. D. S. Cameron, the president, in the chair, the following were elected to the membership:

H. T. Howat, W. F. Anderson, J. W. Affleck, R. B. Wilson, H. C. Jeffrey, Suresh Chandra Kapoor, Akaki Ramishvili, Najib Ullah, Muttutamby Vannitamby, George Holden, R. M. Barnes, A. J. Graham, Youssef Fares Sayegh, Indravadan Chhaganlal Mehta, Emmanuel Patrick, Parmatma Parshad Nayar, M. W. Browne, Tushar Kanti Nag, Mohamed Emad Abbas Fadli, Reginald Ba Pe, Tit Shing Ip, Dorabji Minocher Joshi (Godrej), Walter Sharwan Anandpati Singh, D. B. E. Quamina, Dorrit V. M. Box, J. W. Kibukamusoke, Philip Lanzkowsky, Tapanendra Dhirendra Lahiri, Shyam Sunder Dalmia, Arvind Sadashiv Godbole, Alice Shun-haan Poon, A. H. Laing, Md. Fazle Rabbee, Roy Summerly, Ashis Kumar Chakravarty, Alfred Chickwe Ikeme, Madhu Ratilal Mody, Oon Swee Yeoh, Cecil Chin Hin Chew, Syed Hamid Shafqat, Chaman Lal Anand, W. D. Murray, Gillian M. Watkins, Asuquo Udo Antia, Phyllis M. Fulton, D. A. Stuart-Smith, George Dunea, Khursheed Nowrojee Jeejeebhoy, J. W. Prineas, Adisha Gopal Krishna, Israel Purushotham Sukumar, K. D. Buchanan, Oladipo Olujimi Akinkugbe.

The James Mackenzie medal for 1961 has been awarded to Dr. George Watson.

Royal College of Surgeons of Edinburgh

At a meeting on May 5, with Prof. John Bruce, the president, in the chair, the following were admitted to the fellowship:

Ijaz Chaudhary Ahsan, Husni Abdul-Baki Alusi, Darius Manek Anklesaria, Prabhakar Gopal Apte, Bisheshwar Nath Bhargava, I. H. Brozin, Alexander Cameron, Satya Brata Datta Choudhury, G. J. A. Clunie, F. J. Collins, D. T. Cousins, Roy Dalgleish, Thomas Duncar, W. R. Edwards, W. N. Etheridge, Paul Field, Nasreen Firdous, Hugh Forrest, Asok Kumar Ghosh, Harry Gordon, W. J. H. Graham, Maher Fahmy Guirguis, Shankar Nath Gupta, R. M. Hackett, R. W. Irvine, Chitta Ranjan Josh, Sebastian Kakule Kyalwazi, K. F. Kyle, C. F. Leber, R. A. Long, J. J. Maccabe, J. A. McHardy, Ebrahim Badruddin Mamoowala, K. L. G. Mills, Nrisingha Das Mukherjee, G. C. Nelson, W. J. Newlands, Hashim Abdul Rahman, S. T. Sundara Raj, Debashis Saha, Baldev Prakash Sethi, Surendra Bhogilal Shah, Anjani Kumar Sharma, R. L. Smith, J. A. Southam, P. F. M. Warlow, L. H. Wright, N. L. Wright, Ahmed Abdel Aziz Yacoub, Syed Asghar Zaheer.

Middlesex Hospital Medical School

Sir William Ogg will give a Sanderson Wells lecture on Tuesday, June 6, at 4.15 P.M., at the hospital, London, W.1. He will speak on soils, crop nutrition, and health.

British Epilepsy Association

At the annual general meeting of this Association on May 4 Dr. Karl-Axel Melin, of Stockholm, spoke on the medical treatment of epilepsy in Scandinavia.

Oliver Bird Lecture

Dr. A. S. Parkes will give this lecture on Tuesday, June 20, at 5 P.M., at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1. He will speak on the biological control of conception.

Imperial Cancer Research Fund

On Thursday, May 25, at 5 P.M., at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, at the invitation of the Fund, Mr. Denis Burkitt will give a lecture on a Lymphoma Syndrome in African Children.

South West Metropolitan Regional Hospital Board

The following have been awarded prizes in the board's 1959 competition:

Consultants and S.H.M.O.s.—Dr. J. A. S. Amos.
Senior registrars, registrars, and J.H.M.O.s.—Mr. P. R. French, Dr. Anne Hunter, Dr. J. G. Pritchard.

Regional Hospitals' Consultants and Specialists Association

At the annual dinner, held at the Guildhall, on May 4, Lord Taylor proposed the toast of The Association and Dr. Victor Cotton Cornwall, the president, replied. The Guests was proposed by Mr. Leonard Lancaster and Sir Arthur Porritt replied.

Postgraduate Medical School of London

On May 3 Mr. Harold Macmillan, the Prime Minister, opened the Wolfson Institute at the Postgraduate Medical School. The Institute, towards whose cost Mr. Isaac Wolfson contributed £150,000, contains a large lecture-theatre (450 seats) and two smaller lecture-theatres (160 and 60 seats), dining area, doctors' club, and other rest and recreation rooms. The school needs £2 million for further buildings—notably a new laboratory block—and an appeal launched in 1956, which raised £$\frac{3}{4}$ million, is to be renewed.

Resettlement of the Disabled in a Changing Society

The British Council for Rehabilitation of the Disabled is to hold a course on this subject from July 18 to 20 at the University of Liverpool. Lord Cohen of Birkenhead will give the presidential address and other medical lecturers will be Dr. Alwyn Smith, Dr. J. G. Sommerville, Dr. R. M. Heggie, and Dr. R. O. Murray. Enrolment forms may be had from the council, Tavistock House South, Tavistock Square, London, W.C.1.

International Symposium on Audiosurgery

This symposium is to be held from Aug. 2 to 4 in Madrid, under the chairmanship of Dr. Francisco Antoli-Candela. The programme will include discussions on the audiosurgery of the congenital defects of the ear, the chronic suppurative processes of the ear and their sequelæ, otosclerosis, and surgery of the facial nerve. Dr. Terence Cawthorne and Dr. Francis McGuckin are members of the organising committee. Further particulars may be had from Dr. A. Juderias, Centro Nacional de Especialidades Quirurgicas, Ciudad Universitaria, Madrid.

Stroke Rehabilitation

The Chest and Heart Association are to hold a conference on this subject on Thursday, June 22, at 10 A.M., at the Guildhall, London, E.C.2. The chairman will be Prof. C. Bruce Perry and the medical speakers will include Dr. Lindsey Batten, Dr. John Marshall, Dr. W. Linford Rees, Dr. W. F. Dunham, Dr. T. H. Howell, and Dr. F. S. Cooksey. Further particulars may be had from the organising secretary of the conference, Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1.

Queen Elizabeth College

On May 9 Queen Elizabeth the Queen Mother, chancellor of the University of London, opened the new laboratories at the college which are to be named after Sir John Atkins, F.R.C.S. Sir John, who was largely responsible for the foundation of the college and was for thirty-six years chairman of the council, is still a member of the governing body.

The new building, which was designed by Messrs. Adams, Holden & Pearson, houses the departments of biology, microbiology, and nutrition, and on part of the top floor there is a self-contained isotope unit for the use of any department needing to work with radioactive materials.

International Symposium on Hospital Architecture

Doctors and architects will meet in Weimar from Oct. 4 to 6 to discuss prototypes for a general hospital to serve a population of 100,000. Further particulars may be had from Prof. E. Marcusson, Institut für Sozialhygiene, Akademie für Sozialhygiene, Arbeitshygiene und Ärztliche Fortbildung, Berlin-Lichtenberg, 4, Nöldnererstrasse 40-42.

Japan Association for Study of Congenital Anomalies

This Association, which has recently been founded, would welcome communications from foreign scientists. These may be sent to Prof. Hideo Nishimura, department of anatomy, Faculty of Medicine, Kyoto University.

Absent Doctor Fined

The Glamorgan executive council have approved a fine of £1000 on a doctor who is said to have been absent from his practice while attending a dental course at the University of Sheffield.

Major-General L. T. Furnivall has been appointed honorary surgeon to the Queen in succession to Lieut.-General Sir Alexander Drummond, who has retired.

The Central Council for Health Education has appointed Mr. M. G. Schofield to direct a three-year research project into the problems of adolescence.

A series of lectures and clinicopathological meetings are being held at the Brook General Hospital, Shooters Hill, London, S.E.18, and Lewisham General Hospital, S.E.13, on Wednesdays at 5.45 P.M., until July. On May 17, at the Brook General Hospital, Dr. Peter Wolf will speak on intravascular clotting.

A committee meeting of the Group for Representation of the Views of Clinical Psychiatrists will be held on Thursday, May 18, at 5.30 P.M., at Tavistock House North, Tavistock Square, W.C.1.

On Thursday, May 25, at 6.15 P.M., at the Institut Français du Royaume-Uni, Queensberry Place, London, S.W.7, Dr. Alfred Tomatis of Paris will give a lecture on *Phonation et Audition*, describing his work on the relation between hearing and speech. The lecture is to be in French and admission will be free.

A draft British Standard for sizes of medical X-ray film is now being circulated for technical comment to industry and others concerned. All communications should be addressed to Mr. H. Halkyard at the British Standards Institution, 2, Park Street, London, W.1.

Appointments

HARRIS, L. H., M.D. Lond., M.R.C.P.E.: consultant chest physician, Liverpool and district eastern hospital group and Aintree Hospital.
HOSKING, D. J., M.B. Lond., D.P.H.: senior assistant M.O., Nottingham.
KELLY, A. V., M.B. Belf., M.R.C.P.I., D.P.M.: consultant psychiatrist, Rainhill and Park Hospitals.
JOSEPH, M. C., M.D. Cantab., M.R.C.P., D.C.H.: consultant physician, children's department, Guy's Hospital, with duties at Evelina Hospital, London.

Manchester Regional Hospital Board:

DAVEY, A. C. C., M.B. Manc.: part-time consultant venereologist, Salford hospital group.
PARBROOK, MARGARET J., M.B. Durh., D.A.: assistant anæsthetist, North Manchester hospital group and Booth Hall (children's) Hospital.
SEIGLEMAN, MERTON, M.R.C.S., D.A.: part-time assistant anæsthetist, Blackburn and district hospital group.

The Hospital for Sick Children, Great Ormond Street:

D'SOUZA, CHARMAINE M., M.B. Delhi, D.C.H.: A.R.M.O., Tadworth Court, Tadworth.
KAPSALAKIS, Z., M.D.: resident registrar, neurological and neurosurgical department.
O'GARRA, MARGARET M. R., M.B. Lond., D.C.H.: house-physician.
TEMPANY, EDWARD, M.B. N.U.I., M.R.C.P.I., D.C.H.: medical registrar.